ANNEX XV RESTRICTION REPORT

PROPOSAL FOR A RESTRICTION

IUPAC NAME(S): **N, N-DIMETHYLFORMAMIDE**

SUBSTANCE NAME: **DIMETHYLFORMAMIDE (DMF)**

EC NUMBER: **200-679-5**

CAS NUMBER: **68-12-2**

CONTACT DETAILS OF THE DOSSIER SUBMITTER:

PIETRO PISTOLESE
MINISTRY OF HEALTH
VIA G. RIBOTTA 5
00144 ROME.- ITALY

DATE: **15th JANUARY 2015**

Non-Confidential Version

In this version, the confidential information has been deleted.

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Part A. Proposal

A.1. Proposed restrictions

A.1.1 The identity of the substance

The substance **N,N-dimethylformamide** is a mono constituent substance (organic origin) having the identifiers as listed in table A1. The restriction dossier shall apply to N,N-dimethylformamide whatever its purity. Throughout the proposal the public name Dimethylformamide or its abbreviation DMF is used.

Table A1. Substance identity

EC number:	200-679-5
EC name:	N,N-dimethylformamide
CAS number:	68-12-2
CAS name:	Formamide, N,N-dimethyl-
IUPAC name:	N,N-dimethylformamide
Index number:	616-001-00-X
Molecular formula:	C_3H_7NO

A.1.2. Scope and conditions of restriction

DMF may only be manufactured and used if it can be assured that under normal operating conditions the exposure will remain below the proposed harmonized DNEL for inhalation exposure of 15 mg/m^3. Additionally, DMF may only be manufactured and used if dermal exposure is avoided with protective clothing and gloves, which comply with the requirements of Council Directive 89/686/ECC or other measures. The proposed harmonized DNEL (dermal) of 0.79 mg/kg b.w. day has to be met also. Both DNELs have been derived in the Risk Assessment of DMF within this restriction dossier.

The professional use shall be limited to the use of DMF as laboratory reagent and solvent only. All other non-laboratory professional uses should be forbidden. Professional laboratories (which often belong to industrial settings), including clinical and academic research and testing laboratories are exempt from the ban, because they apply strict occupational controls and chemical hygiene procedures, since the handling of hazardous chemicals, typical in small quantities, is day-to-day routine for this profession and therefore will not have any problems in complying with the above mentioned DNELs. Most of the analytics is related to research & development, quality assurance activities and use as reagents in in-vitro diagnostics. For other professions (e.g. painters) it is doubtful, that the proposed harmonized DNELs can be complied with and thus, should be prohibited.

The exposure levels (inhalation and dermal) must be ensured by the use of preventative and protective measures (e.g. elimination, substitution, enclosure, increased local exhaust ventilation and general ventilation, change in operational conditions, administration, behavior and if needed personal protective equipment) that are applied according to the “hierarchy of control” principle, which is an established concept referred to in the Chemical Agents Directive (Directive 98/24/EC). It should be used at all times when implementing controls to eliminate the hazard or reduce the risk of a hazard. This is done by giving preference to the use of the “engineering controls”. These types of strategies should be used, where possible, because they are less subject to human failure and because they are less disruptive and uncomfortable for people working in the area. Back-up controls (such as PPE and administrative controls) should only be used as a last resort or as a support to other control measures.

Manufacturers and industrial/professional users of DMF must be able to demonstrate at the request of enforcement authorities that they comply with the above restrictions. This can be done by maintaining an adequate exposure monitoring program.

In addition to the restriction of DMF as a substance on its own or in mixtures, significant residual

levels of DMF in articles have been identified (as described in Section B) and should therefore be restricted too. Considering articles for industrial use, acceptable DMF concentrations depend on the kind of article and the intended use pattern. For instance, acrylic fibres are considered safe if the DMF concentration is not higher than 1.5 % by mass (w/w) due to fixation of the compound in the fibre matrix (see section B.9.3.3.1.2). However, this is not the case for gloves used by workers. DMF concentrations of 0.3 % by mass (w/w) in gloves used by workers are not considered safe and therefore the same restriction as for consumer articles will be recommended. It can anyway not be excluded, that gloves for workers are used by consumers. Consumer articles may not be placed on the market if they or parts thereof contain DMF in concentrations higher than 0.1 % by mass (w/w). Moreover, residual DMF was found in consumer articles for children, like toys or clothing. Concentrations of DMF higher than 0.001% by mass (w/w) should therefore be restricted. This concentration level is based on the DMF concentration of 0.1 % which was assessed as unsafe for toys and clothing (see section B.9.3.3.2.2 and B.9.3.3.2.4) and modified by application of an additional assessment factor of 100. This additional assessment factor applied to the concentration level is a default assessment factor used in the derivation of safety hazard levels for health effects by a variety of regulations. In the REACH Regulation a default AF of 100 is suggested to be used as the starting point if no sufficient data exist for dose response and derivation of DNELs is based on mortality data (Box 5 of Appendix R.8-8 of ECHA Guidance R8.). In the case of DMF article assessment, the AF of 100 results from the AF of 10 for uncertainties in the whole database and the AF of 10 related to dose-response. The AF for uncertainties in the whole database is due to insufficient information about safety levels in articles (especially for children) and the AF for dose-response is due to insufficient information about rates of release of certain amounts of DMF from matrix of articles.

Referring to the proposed restriction (see Table A2), a transitional period of two years is recommended.

Table A2. Proposed Restriction

Column 1: Designation of Substance	**Column 2: Conditions of Restriction**
XX. N,N-dimethylformamide EC No.: 200-679-5 CAS No.: 68-12-2	• Manufacturers, importers and downstream users of the substance on its own or in mixtures in a concentration equal or greater than 0.3% shall use in their chemical safety assessment and safety data sheets by [xx.yy.zzzz] a Derived No Effect Level (DNEL) value for workers inhalation of 15 mg/m^3 and a DNEL for workers dermal exposure of 0.79 mg/kg/day. • The professional use is permitted as laboratory reagent or solvent or for in-vitro diagnostics only. All other professional uses outside of laboratories are prohibited. • Articles used by industrial workers may not be placed on the market after [date] if they or parts thereof, contain DMF in concentrations higher than 1.5% by mass (w/w). The concentration limit should be applicable for each individual part of the article and should not be applicable for gloves. • Consumer articles and gloves for workers may not be placed on the market after [date] if they or parts thereof, contain DMF in concentrations higher than 0.1% by mass (w/w). The concentration limit should be applicable for each individual part of the article.

	• Consumer articles for children (e.g. toys, clothing, child care articles) may not be placed on the market after [date] if they or parts thereof, contain DMF in concentrations higher than 0.001% by mass (w/w). The concentration limit should be applicable for each individual part of the article.

A.2. Targeting

The objective is to prevent or to adequately control exposure of DMF to workers and to the general public in order to prevent ill health. Worker exposure information and data on residual content of DMF in articles indicate clear evidence, that risks are arising from some uses and that consumer exposure cannot be ruled out and thus risks need to be controlled.

Therefore, the Restriction Proposal is targeted to the critical uses of DMF in industrial settings, to the "risky" uses in professional applications and to the exposure of workers and consumers through unreasonable residual content of DMF in articles.

A.3. Summary of the justification

A.3.1 Identified hazard and risk

Most of the information was obtained from the registration dossier (Taminco, 2014) and OECD SIDS (2004).

DMF is of low acute toxicity in mammals: LD_{50} rat (oral) 3010 mg/kg bw/day, LC_{50} rat (inhalative, 4 h) > 5900 mg/m^3, LD_{50} rat (dermal) > 3160 mg/kg bw. It was irritating to the eyes of rabbits but not irritating to the skin of rabbits and rats. DMF did not show a sensitizing potential when used as a vehicle in a local lymph node assay. In various repeated dose toxicity studies in rats and mice with chronic and subchronic exposure by inhalation, or in rats treated subchronically by oral administration, the predominant target organ was the liver (NOAEC: chronic inhalation rat: 25 ppm, LOAEC: chronic inhalation mouse: 25 ppm (a NOAEC was not achieved); NOAEC: subchronic inhalation rat 100 ppm, mouse 400 ppm; NOAEL: rat, 90 days 200 ppm, 28 days about 238 mg/kg bw/day). In a 13-week inhalation study with Cynomolgus monkeys no treatment-related effects occurred (NOAEC: 500 ppm). DMF did not induce chromosome aberrations or gene mutations in various test systems in vivo and in vitro. In addition, no increased tumor incidence was found in carcinogenicity studies in rats and mice that were exposed from 25 up to 400 ppm DMF by inhalation for 2 years or 18 months, respectively.

Reproductive toxicity, i.e. reduced fertility and fecundity, was observed in the presence of some general toxicity in a continuous breeding study in mice, when DMF was administered orally in the drinking water at doses ≥ 4000 ppm (appr. 820 mg/kg bw/day). The maximal tolerated dose (MTD) for generalized toxicity was 1000 ppm (appr. 219 mg/kg bw/day) for the F0 and the F1 generation, thus a systemic NOAEL could not be determined. Developmental toxicity (e.g. reduced survival and growth of pups, increase in craniofacial and sternebral malformations) was observed in both off-spring generations at ≥ 4000 ppm. Reduced F2 pup weight was observed at ≥ 1000 ppm (NOAEL F0, F1 fertility: 1000 ppm; NOAEL, F1 developmental toxicity 1000 ppm; LOAEL, F2 developmental toxicity: 1000 ppm).

Developmental toxicity and teratogenicity occurred in rats and rabbits in various studies (inhalation, oral or dermal administration) and in mice (oral administration). In rats embryo-/foetotoxicity and teratogenicity were mostly seen at maternal toxic doses, whereas in mice and in rabbits embryo-/foetotoxicity and teratogenicity occurred also at dose levels without maternal toxicity. However, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF. (Rabbit: NOAEC (inhalation) maternal toxicity and teratogenicity as well as embryo-/foetotoxicity 50 ppm;

NOAEL (oral, gavage) maternal toxicity and embryo-/foetotoxicity 65 mg/kg bw/day, teratogenicity 44.1 mg/kg bw/day; NOAEL (dermal) maternal toxicity and teratogenicity as well as embryo-/foetotoxicity 200 mg/kg bw/day).

With respect to the metabolism of DMF the following conclusion can be drawn: DMF is readily absorbed via all exposure routes. N-hydroxymethyl-N-methylformamide is the main urinary metabolite and to a minor extent, but with greater toxicological relevance the metabolite mono-N-ethylformamide (MMF) occurs which may partially be conjugated to glutathione forming S-methylcarbamoyl-glutathione. The GSH- and its sequel adduct (S-methylcarbamoylcystein and the corresponding mercapturic acid S-methylcarbamoyl-N-acetyl-cysteine) seem to be responsible for developmental toxic effects. At higher doses, DMF inhibits its own metabolism, i.e. the formyloxidation to MMF which precursors the GSH binding. Persons who repeatedly inhaled DMF excreted the mercapturic acid at levels of ~13% of the dose with a total half-life (i.e. DMF biotransformation and excretion) of 23 hours. Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Furthermore, ethanol induces cytochrome P450 2E1 which facilitates the initial hydroxylation of DMF. Thus, exposure to DMF can cause severe alcohol intolerance.

The exposure assessment for DMF at the workplace was performed by using a TIER 1 (exposure modelling) and a TIER 2 (measured data) approach with a respective risk characterisation. For the TIER 1 approach, the software tool CHESAR v2.2 (2013) was used which implements ECETOC TRA v3.1 (2004, 2012) for exposure modelling referring to Human Health. The exposure was calculated for all identified uses as described in section B.1.1 and B.1.2. Due to the fact that relevant measured data from several different industrial sites was available, a TIER 2 assessment was additionally elaborated. By means of the detailed and complex approach for this risk assessment, exposure estimations and risk characterisations take the current state of the art into account. All exposure calculations for Human Health are based on recent information on detailed process conditions provided by the relevant Downstream Users. According to the obtained information, the most common RMMs applied are LEV, gloves, respirators and reduction in exposure time and/or concentrations of DMF used in the process.

In general, exposures resulting from processes under elevated temperatures, processes requiring intensive manual applications and open processes are relatively high which, however, can be addressed by the applied RMMs and OCs. In general, the estimated exposure levels ranged from 0.023 to 3.046 mg/m³ for the inhalation exposure (systemic, long-term). Calculated dermal exposure ranged from 0.007 to 2.7 mg/kg bw/day (systemic, long-term).

The highest exposure levels were estimated for specific processes (PROC 10 – Roller application or brushing; PROC 19 – Hand mixing with intimate contact and only PPE available) which are considered to bear a potential risk towards Human Health. Inhalation exposure was estimated up to 4.568 mg/m³ (systemic, long-term) while dermal exposure was estimated to amount up to 7.072 mg/kg bw/day (systemic, long-term) for these process categories.

By combining the derived DNELs with the exposure estimates, risk characterisation ratios (RCRs) were obtained. Combined RCRs above the trigger values of 1.0 were only calculated for PROC 10 and PROC 19 identifying a potential risk. The fact that RCRs for inhalation are well below 1.0 for most of the industrial applications was further confirmed by the TIER 2 assessment. It is therefore concluded that risks are not sufficiently controlled for the indicated specific processes. It was also shown that applied RMMs and/or OCs for these processes cannot decrease exposure to an adequate level.

Different types of articles used by industrial/professional workers (gloves, acrylic fibres) and consumers (gloves, sports shoes, toys) are known to contain DMF residues. Consecutively, these articles were subject of the performed article assessment in order to define specific cut-off values which are of acceptable risk for human health. Different approaches for the risk assessment were followed. Exposure calculations were performed by applying modified algorithms or by using software tools such as ECETOC TRA v3 and ConsExpo v5. The assessment of possible risks was conducted by calculating RCRs. In this case, only combined RCRs below 1.0 were generally considered to bear an acceptable risk. However, for RCRs between 1.0 and 0.5 additional exposure reduction should be sought.

Gloves containing DMF residues of 0.1 % w/w were assessed to be of acceptable risk for industrial/professional workers and consumers. The same cut-off value applies for sports shoes used by consumers. Articles used by children (sports shoes, slimy toys) bear an unacceptable risk to human

health - even at low DMF concentrations such as 0.1 % w/w. Referring to acrylic fibres used by industrial workers in the textile industry, DMF residuals up to 1.5 % w/w were considered to be of acceptable risk.

A.3.2 Justification that action is required on a Community-wide basis

The main reason for acting on a Community-wide basis is the protection of human health from the adverse effects of DMF due to its reprotoxic (Category 1B) properties. Based on information taken from the registration dossier, there is strong evidence that DMF is potentially used in all EU Member States and that in some industrial settings occupational exposure results in unacceptable risk, for the general worker population and for pregnant workers specifically. Action on a Community-wide basis is required to prevent unacceptable risks from DMF. Moreover, it was demonstrated, that consumers can be exposed through articles containing residual content of DMF, up to gram-level.

According to the EU's Treaty, free movement of goods needs to be guaranteed in order not to distort the internal market. Therefore, acting on a Community-wide basis ensures equal treatment of both - EU producers and importers. Furthermore, it gives a clear signal to non-Community suppliers and provides a "level playing field" by preventing competition distortion and allows equal protection of human health across the EU.

Additionally, DMF has been included in the REACH Candidate List and was recommended by ECHA (2014) for entry into the Authorisation List. Hence, measures for this substance have already been initiated on an EU-wide basis and consequently any additional measures should be conducted on the same level.

Furthermore, two potential substitutes of DMF (DMAC and NMP, see Section C) meet as well the criteria for classification as toxic for reproduction (Category 1b) and therefore qualify for inclusion in REACH Annex XIV. DMAC and NMP are both in the SVHC process. For NMP (N-Methyl-2-pyrrolidone) the Netherlands has submitted a Restriction Proposal (RIVM, 2013). Concerning DMAC (N,N-Dimethylacetamide) and its inclusion into Annex XIV, the Commission stated in its very recent Regulation No 895/2014 of 14th August 2014 the following:

"DMAC has similar intrinsic properties to those of N-Methyl-2-pyrrolidone (NMP) and both substances may be considered as potential alternatives for some of their major uses. Currently the chemical substance NMP is the subject of a restriction procedure in accordance with Article 69 of Regulation (EC) No 1907/2006. In view of the similarities of the two substances, both regarding their intrinsic properties and their industrial applications, and in order to ensure that a consistent regulatory approach is warranted, the Commission considers it appropriate to postpone the decision on the inclusion of DMAC in Annex XIV".

Therefore, the Dossier Submitter (DS) requests, that for DMF a consistent approach on EU-wide level is warranted too.

A.3.3 Justification that the proposed restriction is the most appropriate Community-wide measure

DMF is a high production volume substance which has been registered with a total tonnage band of 10.000 - 100.000 t/a. It has also a registered use as intermediate only (see ECHA dissemination database of registered substances). Part of the tonnage is produced in the EU; part of it is imported from non-Community manufacturers. No direct export from the EU has been reported in the registration dossiers. The outcome of the analysis on exposure of workers clearly shows, that for a few specific areas of use, risks are existing on a Community-wide level, which needs to be controlled and eliminated.

Due to its applications, DMF has been found in some articles in significant residual amounts, which provides clear evidence of exposure to workers and consumers. Therefore, articles used by workers

and consumers have been included in the assessment and restrictions on articles appear to be inevitable since risks have been identified.

DMF is an aprotic and medium polar organic solvent with limited technical feasible alternatives and for the fast majority of applications, adequate substitutes are lacking.

- REACH provides two possible instruments to authorities to regulate risks caused by a substance: Restriction and Authorisation.

Six risk management options, five restriction hypotheses and authorization route have been assessed with respect to their effectiveness in reducing the risk, their proportionality to the risk, their practicality and their monitorability. These options differ from each other as regards the scope and have been described in detail in Section E of this dossier and were evaluated for their socio-economic impact in Section F.

RMO 2, RMO 3 and RMO 4 include the establishment of a mandatory occupational exposure limit (OEL) to control the risk at the workplace. However, feedback on the RMOA from Member States and the Commission demonstrates that REACH Annex XVII is not considered being the appropriate regulation for the setting of workplace exposure limits. For this purpose, there is already specific legislation in place, which should be applied (Directive 98/24/EC). An OEL-based restriction could furthermore generate enforceability difficulties and a possible interaction between REACH enforcement authorities and authorities competent for the control of occupational safety. Therefore, the Dossier Submitter is not introducing a mandatory OEL via a restriction, but is giving reference to an existing indicative OEL (IOEL) value to be able conducting a quantitative risk assessment. The existing IOEL has therefore been selected as the most appropriate EU reference value to evaluate workers exposure to DMF. Furthermore, to use IOEL values as reference value for DNELs is in line with ECHA Guidance. Using the term IOEL value is simply to stress the fact that the reference value for risk characterization is not a DNEL simply derived by employing default factors but that a reference value as set by EU Directive 2009/161 was used and respecting the assignment of the Scientific Committee on Occupational Exposure Limits (SCOEL).

As described above, an OEL is outside the methodology of REACH. By definition, an OEL protects the risk by inhalatory exposure only, while the CSR and the Restriction Proposal identified risks from dermal exposure of workers too, for which additional risk management measures need implementation. Therefore, the Dossier Submitter recommends implementing harmonized DNELs for dermal and inhalation exposure. Replacing the OEL terminology by the respective DNELs, the RMOs would read as follows:

- RMO 1 - Complete restriction (ban)
- RMO 2 - Partial Restriction 1
  ($DNEL_{Inhal}$ 15 mg/m^3, $DNEL_{Derm}$ 0.79 mg/kg b.w. day, professional use for laboratories only, residual DMF content in articles 0.1% w/w).
- RMO 3 - Partial Restriction 2
  ($DNEL_{Inhal}$ 15 mg/m^3, $DNEL_{Derm}$ 0.79 mg/kg b.w. day, professional use for laboratories only, residual DMF content in articles 0.3% w/w).
- RMO 4 - Partial Restriction 3
  ($DNEL_{Inhal}$ 15 mg/m^3, $DNEL_{Derm}$ 0.79 mg/kg b.w. day, professional use for laboratories only, residual DMF content in articles 0.5% w/w).
- RMO 5 - Targeted Restriction
  (For uses for which alternatives appear to be readily available, the use of DMF is banned).
- RMO 6 - Authorisation

In terms of reducing the exposure, the easiness of enforcement and monitoring, RMO 1 will be the most effective measure. However, prohibiting the manufacture and use of DMF in all applications through a complete restriction is according to available information not the right measure, because DMF will be substituted by other equally hazardous substances as described in Section C of this report.

Moreover, it can be assumed that industry might cease EU production and use and relocate activities to non-EU countries. Furthermore, it needs to be considered that DMF is a threshold substance, which

means that the toxicological endpoint will have a theoretically identifiable dose threshold and thus a potentially 'safe' level of exposure (ECHA, 2012). Consequently, DMF can be used without causing a risk for human health as long as the threshold is undercut through adequate control of exposure. Due to the identified costs and severe socio-economic impact, the lack of feasible alternatives for most of the uses and considering that the risks can be adequately controlled by the proposed restriction, this RMO is not proportional.

The same applies for the authorisation approach (RMO 6) and is therefore as well not considered to be proportional. Additionally, the authorisation procedure is more costly for both – for applicants and for authorities. If save use is demonstrated, there would be no difference in residual risk, compliance costs or monitoring of implementation, whether the restriction or authorisation route is used. Also, articles cannot be regulated through the authorisation route. Thus, since risks are arising from DMF impurities in articles, the restriction route would need to be followed in addition, which will further increase the costs and adds a layer of complexity related to practicality and monitorability.

For professional uses in most cases a restriction is the only way in which the exposure requirements (DNELs) of the restriction can be met (RMO 5). Therefore, professional uses of DMF should be restricted, apart from the use as laboratory reagent and solvent, where strict occupational controls and chemical hygiene procedures are applied, since the handling of hazardous chemicals is day-to-day routine for this profession.

RMO 2 to RMO 4 are all the same related to the implementation of the two proposed harmonized DNELs (inhalation + dermal). The only difference is the varying residual concentration of DMF in consumer and industrial articles. The different levels of residual content of DMF have been risk assessed for different groups (workers, consumers and children), the results of the evaluation are shown in Sec. B.

Based on the Socio-Economic Analysis in Section F and the results of the articles risk assessment in Section B, a restriction in terms of two mandatory harmonized DNELs (inhalation + dermal), combined with a targeted restriction for professional use and the implementation of limit values for DMF residual contents in articles, is for the Dossier Submitter (DS) the most appropriate Community-wide measure.

Such a restriction would ensure the safe use of DMF by respecting the proportionality principle and ensuring a high level of practicality and monitorability. Moreover, this measure would follow the specified route for managing substances under REACH through a Chemical Safety Assessment by applying Derived No Effect Levels (DNELs).

Part B. Information on hazard and risk

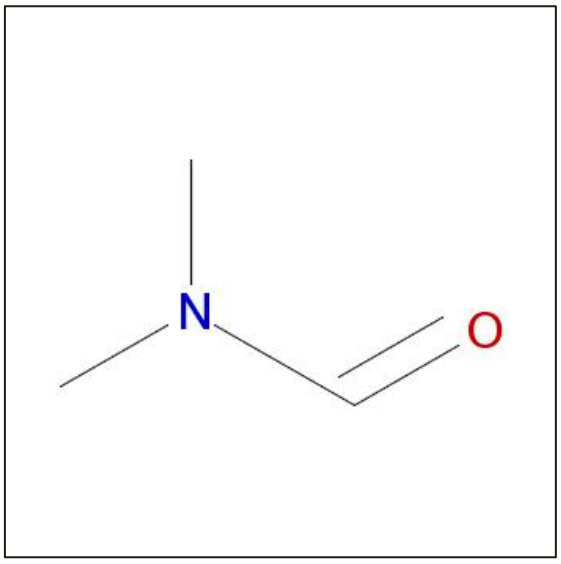
B.1 Identity of the substance and physical and chemical properties

B.1.1 Name and other identifiers of the substance

The substance **N, N-dimethylformamide** is a mono constituent substance (origin: organic) having the following characteristics and physical–chemical properties (see the IUCLID dataset for further details).

The following public name is used: Dimethylformamide.

Structural formula:



B.1.2. Composition of the substance

Name: N, N-dimethylformamide

Description: mono constituent substance
Degree of purity: **Confidential information**

Table B1. Constituents

Constituent	Typical concentration	Concentration range	Remarks
N,N-dimethylformamide EC No.: 200-679-5	**Confidential information**	**Confidential information**	**Confidential information**

B.1.3. Physicochemical properties

DMF belongs to the chemical class of dipolar aprotic solvents having high dielectric constants and high dipolar moments.

Table B2. Physico-chemical properties of DMF

Property	Description of key information	Value used for CSA / Discussion
Physical state	N,N-dimethylformamide is a colourless - yellowish liquid with a faint specific, amine - like odour. The substance origin is organic.	**Value used for CSA:** liquid at 20 °C and 101.3 kPa The description of N,N-dimethylformamide is given by BASF AG (2005) as well as by the peer-reviewed database GESTIS (2005).
Melting / freezing point	Melting point = -61 °C	**Value used for CSA:** -61 °C at 101.3 kPa Experimental data as well as peer-reviewed database report a melting / freezing point of N,N-dimethylformamide of around - 61 °C (Beilstein, 2006; Verschueren, 1983; IPCS, 1991; and Bipp, H., Kieczka, H., 1989).
Boiling point	Boiling point = 152 - 153 °C at 1013 hPa.	**Value used for CSA:** 152 °C at 101.3 kPa The boiling point for N,N-dimethylformamide is given by experimental data as well as by peer-reviewed databases (Beilstein, 2006; IPCS, 1991; Budavari, S., 1996, Bipp, H., Kieczka, H., 1989; Verschueren, 1983).
Relative density	Relative density = 0.94	**Value used for CSA:** 0.94 at 20 °C The relative density for N,N-dimethylformamide is given by the following sources: Beilstein, 2006; Budavari, S, 1996; ICPS, 1991; Bipp, H., Kieczka, H., 1989; BASF AG, 2002, and Verschueren, K., 1983.
Vapour pressure	Vapour pressure = 3.77 hPa at 20 °C	**Value used for CSA:** 3.77 hPa at 20 °C The following sources are found to report the vapour pressure of N,N-dimethylformamide: GESTIS, 2002; IPCS, 1991; Verschueren, 1983; BASF AG, 2002; Beilstein, 2006; and Daubert, T.E., Danner, R.P., 1989.
Partition coefficient n-octanol/water (log value)	Partition coefficient ($logP_{ow}$) = -0.85 at 25 °C	**Value used for CSA:** $logP_{ow}$: -0.85 at 25 °C The partition coefficient is given by the following sources: BASF AG, 1988;

Property	Description of key information	Value used for CSA / Discussion
		ICPS, 1991; and Hansch, C. et al., 1995.
Water solubility	Degree of water solubility is declared as "miscible".	**Value used for CSA:** 1000 g/L at 20 °C Degree of water solubility is declared as "miscible", which corresponds to ca. 1000 g/L. Data sources were: Budavari, S. (1996), BASF AG (2002), IPCS (1991), and Bipp, H, Kieczka, H. (1989).
Flash point	Flash point = 57.5 °C at 1013.25 hPa	**Value used for CSA:** 57.5 °C at 1013 hPa The following sources give details regarding flash point of N,N-dimethylformamide: BASF AG (1979, 2002), Bipp, H., Kieczka, H. (1989), Clayton G.D., Clayton, F.E. (1993), and IPCS (1991).
Autoflammability / self-ignition temperature	Self ignition temperature = 435 °C	**Value used for CSA:** 435 °C at 1013 hPa Data sources used: BASF AG (1979), ICPS (1991), and HSDB (2006).
Dissociation constant	Dissociation constant (pKa) = -0.3	**Value used for CSA:** pKa at 20 °C: -0.3 The pKa value for N,N-dimethylformamide is given by Perrin, D.D. (1972) and Riddick, J.A., Bunger, W.B., Sakano, T.K.(1985).
Viscosity	Viscosity at 20 °C = 0.92 - 0.9248 m Pa s (dynamic) Viscosity at 25 °C = 0.802 m Pa s (dynamic)	**Value used for CSA:** Viscosity at 20 °C: 0.92 mPa · s (dynamic) The viscosity of N,N-dimethylformamide was experimentally determined (Kirk-Othmer, 1991; Bipp, H., Kieczka, H., 1989) and also cited in the peer-reviewed database Beilstein (2006).

B.1.4. Justification for grouping

Not relevant for this proposal.

B.2 Manufacture and uses

B.2.1. Manufacture, import and export of DMF

Table B3. Manufacture

Identifiers	Use descriptors	Other information
M-1: Manufacture of substance	**Environmental release category (ERC):** ERC 1: Manufacture of substances **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 15: Use as laboratory reagent	Tonnage of substance: **Confidential information** Number of sites: **Confidential information**

Table B4. Manufacturing process related to the specified manufacture(s)

Related manufacture(s)	Description of manufacturing process
	Confidential information

No information available on production of articles covered by the specified use(s). However, specific articles which can contain DMF residues are discussed in section B.9.3 of this document.

B.2.2. Uses of DMF

Table B5. Formulation

Identifiers	Use descriptors	Other information
F-2: Formulation of substance	**Environmental release category (ERC):** ERC 2: Formulation of preparations **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing)	Tonnage of substance: **Confidential information** Number of sites: **Confidential information** Substance supplied to that use: As such In a mixture

Identifiers	Use descriptors	Other information
	PROC 15: Use as laboratory reagent **Product Category formulated:** PC 0: Other: not applicable **Technical function of the substance during formulation:** not applicable	

Table B6. Uses at industrial sites

Identifiers	Use descriptors	Other information
IW-3: Industrial use for the production of fine chemicals	**Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates) ERC 6b: Industrial use of reactive processing aids ERC 7: Industrial use of substances in closed systems **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation PROC 15: Use as laboratory reagent **Product Category used:** PC 19: Intermediate PC 20: Products such as ph-regulators,	Tonnage of substance: **Confidential information** Number of sites: **Confidential information** Substance supplied to that use: As such In a mixture Subsequent service life relevant for that use: no

Identifiers	Use descriptors	Other information
	flocculants, precipitants, neutralisation agents PC 21: Laboratory chemicals PC 27: Plant protection products **Sector of end use:** SU 9: Manufacture of fine chemicals SU 8: Manufacture of bulk, large scale chemicals (including petroleum products) SU 17: General manufacturing, e.g. machinery, equipment, vehicles, other transport equipment SU 0: Other: SU 3: Industrial Use **Technical function of the substance during formulation:** Solvents	
IW-4: Industrial use for the production of pharmaceuticals	**Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates) ERC 6b: Industrial use of reactive processing aids ERC 7: Industrial use of substances in closed systems **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent **Product Category used:** PC 19: Intermediate	Tonnage of substance: **Confidential information** Number of sites: **Confidential information** Substance supplied to that use: As such In a mixture Subsequent service life relevant for that use: no

Identifiers	Use descriptors	Other information
	PC 21: Laboratory chemicals PC 29: Pharmaceuticals **Sector of end use:** SU 9: Manufacture of fine chemicals SU 8: Manufacture of bulk, large scale chemicals (including petroleum products) SU 17: General manufacturing, e.g. machinery, equipment, vehicles, other transport equipment SU 20: Health services SU 0: Other: SU 3: Industrial Use **Technical function of the substance during formulation:** Solvents	
IW-5: Industrial use for the production of polymers	**Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates) ERC 6c: Industrial use of monomers for manufacture of thermoplastics ERC 6d: Industrial use of process regulators for polymerisation processes in production of resins, rubbers, polymers ERC 7: Industrial use of substances in closed systems **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent	Tonnage of substance: **Confidential information** Number of sites: **Confidential information** Substance supplied to that use: As such In a mixture Subsequent service life relevant for that use: no

Identifiers	Use descriptors	Other information
	Product Category used: PC 19: Intermediate PC 21: Laboratory chemicals PC 32: Polymer preparations and compounds **Sector of end use:** SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys) SU 12: Manufacture of plastics products, including compounding and conversion SU 0: Other: SU 3: Industrial Use **Technical function of the substance during formulation:** Solvents	
IW-6: Industrial use for the production of textiles, leather and fur	**Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates) ERC 6c: Industrial use of monomers for manufacture of thermoplastics ERC 6d: Industrial use of process regulators for polymerisation processes in production of resins, rubbers, polymers **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) **Product Category used:** PC 1: Adhesives, sealants PC 9a: Coatings and paints, thinners, paint removes PC 23: Leather tanning, dye, finishing,	Tonnage of substance: **Confidential information** Number of sites: **Confidential information** Substance supplied to that use: As such In a mixture Subsequent service life relevant for that use: no

Identifiers	Use descriptors	Other information
	impregnation and care products PC 34: Textile dyes, finishing and impregnating products; including bleaches and other processing aids **Sector of end use:** SU 5: Manufacture of textiles, leather, fur SU 18: Manufacture of furniture SU 0: Other: SU 3: Industrial Use **Technical function of the substance during formulation:** Solvents	
IW-7: Industrial use for the manufacture of non-metallic mineral products	**Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 7: Industrial spraying **Product Category used:** PC 0: Other: Mineral products **Sector of end use:** SU 13: Manufacture of other non-metallic mineral products, e.g. plasters, cement SU 0: Other: SU 3: Industrial Use **Technical function of the substance during formulation:** Solvents	Tonnage of substance: **Confidential information** Number of sites: **Confidential information** Substance supplied to that use: As such In a mixture Subsequent service life relevant for that use: no
IW-8: Industrial use for the manufacture of perfumes / fragrances	**Environmental release category (ERC):** ERC 7: Industrial use of substances in closed systems **Process category (PROC):** PROC 3: Use in closed batch process (synthesis or formulation) PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities **Product Category used:** PC 28: Perfumes, fragrances	Tonnage of substance: **Confidential information** Number of sites: **Confidential information** Substance supplied to that use: As such In a mixture Subsequent service life relevant for that use: no

Identifiers	Use descriptors	Other information
	Sector of end use: SU 9: Manufacture of fine chemicals SU 0: Other: SU 3: Industrial Use **Technical function of the substance during formulation:** Solvents	

Table B7. Uses by professional workers

Identifiers	Use descriptors	Other information
PW-9: Use as laboratory chemical	**Environmental release category (ERC):** ERC 8a: Wide dispersive indoor use of processing aids in open systems **Process category (PROC):** PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 15: Use as laboratory reagent **Product Category used:** PC 21: Laboratory chemicals **Sector of end use:** SU 24: Scientific research and development **Technical function of the substance during formulation:** Solvents	Tonnage of substance: **Confidential information** Substance supplied to that use: As such In a mixture Subsequent service life relevant for that use: no

B.2.3. Uses advised against by the registrants

Table B8. Uses at industrial sites

Identifiers	Use descriptors	Other information
IW-3: Industrial use for the production of fine chemicals	**Process category (PROC):** PROC 19: Hand-mixing with intimate contact and only PPE available. **Technical function of the substance during formulation:** Solvents	
IW-4: Industrial use for the production of pharmaceuticals	**Process category (PROC):** PROC 19: Hand-mixing with intimate contact and only PPE available. **Technical function of the substance during formulation:** Solvents	
IW-5: Industrial use for the production of polymers	**Process category (PROC):** PROC 10: Roller application or brushing **Technical function of the substance during formulation:** Solvents	

The provided uses advised against are not explicitly based on the respective Identified Use itself. Considering the risk assessment for DMF (please refer to Chapter B9.1 of this document), specific processes were identified which bear a potential risk for human health. In conclusion, uses advised against only refer to these processes.

B.3 Classification and labelling

B.3.1. Classification and labelling in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)

Substance: N, N-dimethylformamide

Implementation: EU

State/form of the substance: liquid

Classification

The substance is classified as follows:

Table B9. Classification and labelling according to CLP / GHS for physicochemical properties

Endpoint	Hazard category	Hazard statement	Reason for no classification	CSR section*)
Explosives:			conclusive but not sufficient	6.1

Endpoint	Hazard category	Hazard statement	Reason for no classification	CSR section*)
			for classification	
Flammable gases:			conclusive but not sufficient for classification	6.2
Flammable aerosols:			conclusive but not sufficient for classification	6.2
Oxidising gases:			conclusive but not sufficient for classification	6.3
Gases under pressure:			conclusive but not sufficient for classification	
Flammable liquids:			conclusive but not sufficient for classification	6.2
Flammable solids:			conclusive but not sufficient for classification	6.2
Self-reactive substances and mixtures:			conclusive but not sufficient for classification	
Pyrophoric liquids:			conclusive but not sufficient for classification	6.2
Pyrophoric solids:			conclusive but not sufficient for classification	6.2
Self-heating substances and mixtures:			conclusive but not sufficient for classification	
Substances and mixtures which in contact with water emit flammable gases:			conclusive but not sufficient for classification	6.2

Endpoint	Hazard category	Hazard statement	Reason for no classification	CSR section*)
Oxidising liquids:			conclusive but not sufficient for classification	6.3
Oxidising solids:			conclusive but not sufficient for classification	6.3
Organic peroxides:			conclusive but not sufficient for classification	
Corrosive to metals:			conclusive but not sufficient for classification	

*) Justification for (non)classification can be found in the CSR section indicated

Table B10. Classification and labelling according to CLP / GHS for health hazards

Endpoint	Hazard category	Hazard statement	Reason for no classification	CSR section*)
Acute toxicity - oral:			conclusive but not sufficient for classification	5.2.3
Acute toxicity - dermal:	Acute Tox. 4*	H312: Harmful in contact with skin.		5.2.3
Acute toxicity - inhalation:	Acute Tox. 4	H332: Harmful if inhaled.		5.2.3
Skin corrosion / irritation:			conclusive but not sufficient for classification	5.3.4 and 5.4.3
Serious damage / eye irritation:	Eye Irrit. 2	H319: Causes serious eye irritation.		5.3.4
Respiration sensitization:			conclusive but not sufficient for classification	5.5.3
Skin sensitisation:			conclusive but not sufficient for classification	5.5.3
Aspiration hazard:			conclusive but not sufficient for classification	5.2.3
Reproductive Toxicity:	Repr. 1B Specific effect: H360D "May damage the unborn child". Route of exposure: Oral (oral, dermal and inhalation)	H360: May damage fertility or the unborn child <state specific effect if known > <state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard>.		5.9.3
Reproductive Toxicity: Effects on or via lactation:			conclusive but not sufficient for classification	5.9.3
Germ cell mutagenicity:			conclusive but not sufficient for classification	5.7.3
Carcinogenicity:			conclusive but not sufficient for classification	5.8.3

Endpoint	Hazard category	Hazard statement	Reason for no classification	CSR section*)
Specific target organ toxicity - single:			conclusive but not sufficient for classification	5.2.3 and 5.3.4
Specific target organ toxicity - repeated:			conclusive but not sufficient for classification	5.6.3

*) Justification for (no)classification can be found in the CSR section indicated

Table B11. Classification and labelling according to CLP / GHS for environmental hazards

Endpoint	Hazard category	Hazard statement	Reason for no classification	CSR section*)
Hazards to the aquatic environment (acute/short-term) :			conclusive but not sufficient for classification	7.6
Hazards to the aquatic environment (long-term):			conclusive but not sufficient for classification	7.6
Hazardous to the ozone layer:			conclusive but not sufficient for classification	7.6

*) Justification for (no) classification can be found in the CSR section indicated (submitted February 2014)

Labelling

Signal word: Danger

Hazard pictogram:

GHS07: exclamation mark

GHS08: health hazard

Hazard statements:

H360: May damage fertility or the unborn child <state specific effect if known > <state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard>
(Specification of hazard statement: H360D)

H332: Harmful if inhaled.

H319: Causes serious eye irritation.

H312: Harmful in contact with skin.* (minimal classification)

Precautionary statements:

P261: Avoid breathing dust/fume/gas/mist/vapours/spray.

P280: Wear protective gloves/protective clothing/eye protection/face protection.

P302+P352: IF ON SKIN: Wash with plenty of soap and water.

P304+P340: IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for

breathing.

P305+P351+P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

P308+P313: IF exposed or concerned: Get medical advice/attention.

B.3.2. Classification and labelling in classification and labelling inventory/Industry's self classification(s) and labelling

B.3.2.1. Classification and labelling in Annex I of Directive 67/548/EEC

Not relevant.

B.3.2.2. Self classification(s)

No relevant information available.

B.3.2.3. Other classification(s)

No relevant information available.

B.4 Environmental fate properties

Environmental fate properties are considered not relevant for this restriction dossier.

B.5 Human health hazard assessment

The summarized data for the human health hazard endpoints were adopted from the registration dossier, CSR and/or OECD SIDS (2004). Additionally, some recent literature data were used as well. The study reports of the key studies were kindly received from the lead registrant for the endpoints repeated dose toxicity and reproduction and developmental toxicity. The data on toxicokinetics, dermal absorption and human case studies were extracted from the articles publicly available. Those studies are described in more detail since it was considered that the dermal absorption, repeated dose toxicity for the general worker population and the developmental toxicity endpoint for pregnant workers are the most critical endpoints. The Dossier Submitter evaluated the studies and adapted when considered necessary the NOAELs and LOAELs for the individual studies. Further, this Annex XV restriction dossier is targeted to the use of DMF in industrial settings and by professionals. Therefore, for the relevant endpoints, the Point of Departure (POD) and DNELs are derived for the dermal and inhalation routes as the oral route of exposure is considered to be negligible for workers.

B.5.1. Toxicokinetics (absorption, metabolism, distribution and elimination)

The information on the toxicokinetics was obtained from the registration dossier and OECD SIDS and is summarized below:

- There are numerous human and animal studies available using the dermal, inhalation, oral i.p. or i.v. routes;
- DMF is readily absorbed via all exposure routes in human beings and animals. Dermal absorption from the vapour phase may even exceed pulmonary absorption;
- DMF and its metabolites are rapidly and uniformly distributed throughout the organism, predominantly in the blood and kidneys;
- DMF is metabolised by hydroxylation to its major metabolite N-hydroxymethyl-N-methylformamide which can further be oxidised to mono-N-methylformamide (MMF). MMF has a greater toxicological relevance because of conjugation to glutathione forming S-methylcarbamoylglutathione. The last seem to be responsible for hepatotoxic and developmental toxic effects;
- DMF and it metabolites are excreted primarily via the urine and to a lesser extent via faeces and expired air;
- At higher doses, delayed biotransformation rates were observed (DMF inhibits its own metabolism);
- Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Therefore, exposure to DMF can cause severe alcohol intolerance in humans.

B.5.1.1. Non-human information

Brief description of results of toxicokinetic studies in animals are summarised below.

International DuPont Co., 1966

Two experiments in rats were conducted. In the experiment 1, identity of the major metabolite of DMF was proven. Twenty-four rats were given 300 mg of DMF subcutaneously on Monday and again on Wednesday. Urine was collected from Monday to Friday. In the experiment 2, blood and urine levels of the metabolite were determined. A series of rats were given, subcutaneously (s.c.), a single injection of 0.6 mL of a 50 % solution of DMF and sacrificed at intervals over a period of 64 hours to measure the blood concentration of MMF. The total urine voided during each interval was also collected for analysis. Three samples of urine from workmen handling DMF at the plant were also collected in this study. The samples as received were analyzed by gas chromatography. Control urine was similarly treated and analyzed.

After single s.c. dose, 3 ppm of MMF metabolite was detected in the blood within the first hour after the dosing. The concentration increased until 24 hours after administration and then began to decrease. No MMF was detected in the blood after 48 hrs. About 75 % of total administered DMF was excreted in the urine as DMF and MMF. The primary component in the urine of DMF was identified as N-methylformamide (MMF) by its retention time and confirmed by mass spectrometry using time of flight analysis.

In the human worker urine samples, a component with the same retention time as MMF was detected in all three samples. When analyzed by gas chromatography, MMF, but not DMF, was identified in the extract by its relative retention time. The amount of MMF in the three urine samples was 10, 20, and 60 ppm.

International DuPont Co., 1971

C^{14}-labeled DMF in corn oil at two dose levels (approximately 36 mg/kg or 350 mg/kg) was administered to rats by intragastric route of exposure (1971). The animals were placed in the metabolic cages. Exposition to dried and CO_2-free air was subsequent done. After 72 h the animals were sacrificed. Tissue, urine and feces samples were analyzed for total radioactivity. Each of the three 24-hour intervals for exhaled air collection contained six samples, three for 0-7 hours and three for 7-24 hours. After the 72-hour period, blood was removed from the heart under light anesthetic. The animals were then killed and the following organs removed: brain, heart, liver, testes, spleen, kidneys, lungs, portions of fat and muscle, and the gastro-intestinal tract; the eviscerated carcass was also stored. All the tissues were then frozen. The tissue samples, 24 - hour samples of urine and faeces and the various air traps were analyzed for total radioactivity by combustion-liquid scintillation counting technique to determine the distribution of radiolabeled DMF and/or its metabolites.

Urine was the major excretion route. The predominant metabolite was monomethylformamide. Smaller amounts of radiolabeled formamide and a minor unknown metabolite were also detected. Small amounts of non-radiolabeled formaldehyde were also found in the urine at both doses due to the oxidation of the methyl groups as they were removed from the ^{14}C-labeled portion of the molecule. No DMF was detected. About equal amounts of radiolabeled DMF, monomethylformamide, formamide and the unknown metabolites were contained in the faeces based on GC analysis of the 0-24 hour faeces sample from the rat receiving the highest dose. Faeces samples were not examined further because of the low amount of ^{14}C-activity present. The expired ^{14}C was mostly $^{14}CO_2$, about 10 % of the total accountable radioactivity with only about 0.75 % being trapped in the medium as monomethylformamide. Analysis of a water homogenate of the liver sample from the rat receiving the higher dosage of ^{14}CDMF showed about equal amounts of formaldehyde and the unknown metabolite in this tissue at the time of sacrifice, 72 hours after dosing. Total percent radioactivity recovered in all tissues samples was 2.5 % for the lower dose rat and 3.2 % for the high dose rat.

Sheveleva et al., 1977

DMF has been shown to cross the placenta after exposure of rats by inhalation.

Eben and Kimmerle, 1976; Hanasono et al., 1977

A greatly delayed excretion of monomethylformamide in urine, due to delayed biotransformation of DMF after combined exposure to ethanol and DMF, has been demonstrated in experimental animals, human volunteers and persons occupationally exposed (Eben and Kimmerle, 1976). However, the metabolism of ethanol was also influenced by N,N-dimethylformamide. Exposure to DMF seems to inhibit the ethanol oxidation, what can explain the observed alcohol intolerance in workers. In another study confirming these results, accumulation of acetaldehyde in blood has been demonstrated in rats which were given ethanol 18 hours after exposure to DMF (Hanasono, 1977). In details, DMF pretreatment with a dose of 2 mmol/kg impaired the oxidative metabolism of acetaldehyde, whereas a larger dose of 20 mmol/kg interfered with the primary oxidative step which converts ethanol to acetaldehyde.

Lundberg et al., 1981; 1983

In a study, DMF and its biotransformation products monomethylformamide (MMF) and formamide (F) were administered intraperitoneally to rats (Lundberg et al., 1981). Serum levels of sorbitol dehydrogenase (SDH) elevated after exposure to DMF and MMF (each separately and simultaneously), but not after exposure to F. Liver histology proved elevated SDH levels to be an indication of liver necrosis. These findings suggest that DMF hepatotoxicity is mediated by a degradation product of MMF and that DMF delays the hepatotoxic effect induced by MMF. In the next study, the authors exposed rats to two DMF air concentrations: (2250 (high) and 565 (low) ppm, corresponding to about 6.82 mg/L or 1.71 mg/L, respectively, for 4 h (Lundberg et al., 1983). Concentrations of DMF and the biotransformation product MMF were measured in blood and some tissues at 0, 3, 6, 20, and 48 hours after the end of exposure. MMF concentrations 0 and 3 h after the end of the high exposure were generally lower than MMF concentrations at the same time after the low exposure. The results suggested again that DMF biotransformation to MMF is delayed after the high exposure. This could be a reason of hepatotoxicity of DMF. Additionally, both DMF and MMF were distributed fairly uniformly over the different tissues, though blood and kidneys usually had the highest concentrations.

Scailteur et al., 1984; Scailteur and Lauwerys, 1984 (a, b); Brindley et al., 1983

The authors studied the biotransformation of DMF *in vivo* in male and female SD rats after i.p. treatment, and *in vitro* in various rat organs and tissues (Scailteur et al., 1984). Their results demonstrated that DMF-OH was the main metabolite in rat *in vivo*. In a previous study, hydroxylation of the methyl group of DMF to form N-hydroxymethyl-N-methylformamide (DMF-OH) was supposed also to be the main metabolic pathway of DMF in rodents (Brindley et al., 1983). Further results of these studies are: when ^{14}C-DMF was administered to mice, 83 % of the dose was recovered in urine within 24 h. Of this amount, 56 % was excreted as N-hydroxymethyl-N-methylformamide and 5 % as unmetabolized DMF; 3 % of the dose administered was excreted as N-(hydroxymethyl)-formamide (NMF-OH) or formamide and 18 % as unidentified metabolites. NMF-OH, determined as formamide by GC, was quantitatively less important urinary metabolite also in the study of Scailteur et al. (1984). In male and female rats the liver was the main organ of biotransformation. The total amount of metabolites of DMF excreted in urine was identical in both sexes, but females excreted more unchanged DMF than the males (Scailteur et al., 1984). In the following-up study, N-methylformamide (NMF) was found to be is not a product of DMF-OH biotransformation but is directly formed from DMF (Scailteur and Lauwerys, 1984a). Comparison of the acute toxicity of DMF, DMF-OH and NMF shows that NMF is more toxic than DMF-OH, which is itself more toxic than DMF (Scailteur and Lauwerys, 1984b).

Hundley et al., 1993a

In another study, hole-body inhalation exposures to N,N-dimethylformamide (DMF) were conducted with rats and mice. The exposure concentrations were 10, 250, and 500 ppm DMF. The exposure routines consisted of single 1-, 3-, or 6-hour exposures and ten 6-hour exposures (ten exposure days in 2 weeks). For each sampling interval 4 rats and 4 mice were used for blood and/or urine collection. Following single exposures of either 1, 3 or 6 hour duration, blood samples were collected 0.5 hour post-exposure. In the animals exposed for a single 6-hour period, blood samples were also taken 1, 2, 4 , 6, 8 , 12, and 24 hours post-exposure. Urine samples were collected from the rodents used for the 24 hour blood samples. In the multiple exposure portion of the experiment, rats and mice were exposed 6 hours per day, 5 days per week (no exposures were conducted on the weekend following the 5th exposure) for 2 weeks. Blood and urine samples were collected after the final exposure according to the same schedule as presented above for the animals receiving a single 6-hour exposure. Areas under the plasma concentration curve (AUC) values were determined following exposure for DMF and “N-methylformamide” (“NMF” represented N-methylformamide plus N-(hydroxymethy1)-N-methylformamide (DMF-OH)).

The DMF AUC values increased 8- and 29-fold for rats and mice, respectively, following single six-hour exposures to 250 and 500 ppm DMF. These data are indicative of saturation of DMF metabolism. Peak "NMF" plasma concentrations for rats and mice, following single 6-hour exposures, did not increase as DMF exposure concentrations increased from 250 to 500 ppm. In addition, the

"NMF" plasma levels in rats following a single 6-hour 500 ppm DMF exposure did not decay by 24 hours post exposure. These "NMF" plasma data also indicate saturation of DMF metabolism. Multiple exposures to 500 ppm DMF resulted in a 3- and 4-fold reduction in DMF AUC values for rats and mice, respectively, compared to AUC values following a single six-hour 500 ppm DMF exposure. This indicates enhanced metabolism of DMF resulting from multiple 500 ppm DMF exposures and together with saturation of DMF metabolism suggest using exposure levels below 500 ppm in a chronic bioassay. Selected plasma samples were simultaneously assayed for NMF and DMF-OH. The "NMF" values consisted of between 30 to 60 percent DMF-OH depending upon the exposure group (conversely NNF represented 30 to 60 percent of the “NMF" levels). Urinary analysis of all samples revealed DMF-OH represented over 90 percent of the summed DMF, DMF-OH and NMF quantities.

International DuPont Co., 1990

This is a study with the similar study design as that by Hundley et al. (1993a). It seems that the same results are presented but there is additional information about investigations in organs of rats. In details, four animals from each group (exposure regimes were the same as by Hundley et al., 1993a) were anesthetized after 5 days of exposure and implanted subcutaneously with an osmotic minipump, which provides a 7-day constant release of [3H]thymidine and then exposed for an additional 5 days. On the sixth day (24 hours post exposure), all animals designated for cell proliferation studies were sacrificed. The liver, testes, kidney, nasal tissues, tracheas, lung, and prostate were collected 24 hrs after exposure to assess cell proliferation and morphological changes. There were generally four replicates for each analysis at each time point. For the cell proliferation tests tissues were collected and processed to slides. [3H]thymidine incorporated into the DNA of replicating cells was visualized. Approximately 2000 cells were counted per slide. Labelling index was calculated as the percentage of replicating cells. Statistically significant increases in the labelling index of lung were observed in the 10 ppm and 500 ppm groups. However, there was no dose-response between 10 ppm and 500 ppm groups. No effects were observed in rat liver, prostate, and nasal tissues. Results suggested that the lung might be a potential target organ of DMF exposure.

Kestell et al. (1985, 1986a,b, 1987), BASF AG, 1990

N-hydroxymethylformamide and methylamine were identified in the urine of CBA/CA mice dosed by radioactive DMF (1985). Formate was not a urinary metabolite of N-methylformamide. Additionally, the major route of elimination was found to be via the kidneys although a substantial quantity (39 % of the dose) was eliminated via the lungs as CO_2. In a follow-up study, N-(hydroxymethyl)-N-methylformamide was proved to be a major urinary metabolite of DMF in mice (1985a). This was confirmed by proton NMR. Dimethylamine and methylamine were found to be minor metabolites of DMF. In the next study, a new urinary metabolite of DMF (N-acetyl-S-(N-methyl-carbamoyl)cysteine) was identified that was suggested to be a precursor(s) that may well be responsible for the hepatotoxicity in rodents (1986b; BASF AG, 1990). In the third follow-up study, Kestell et al. (1987), examined the hepatotoxic potential of DMF and other structurally similar analogs in mice. The results suggested that 2 metabolic pathways of N-alkylformamides can be distinguished: hydroxylation of the-carbon of the N-alkyl group and oxidation of the formyl moiety; the former pathway presumably constitutes a detoxification route, and the latter may well be associated with hepatotoxicity, and affords a glutathione conjugate, S-(N-methylcarbamoyl) glutathione, eventually excreted in the urine as mercapturate (N-acetyl-S-(N-methyl-carbomoyl) cysteine = AMCC). AMCC is supposed to be indicative of bioactivation of DMF toward a reactive species associated with hepatotoxicity.

Pearson et al., 1990, 1991

It was assumed that DMF can be bioactivated to methyl isocyanate, a reactive species associated with hepatotoxicity. In this regard, in a metabolism study in rats Pearson et al. had identified S-(N-methylcarbamoyl)glutathione, a chemically-reactive metabolite of methylisocyanate which formed conjugates with glutathione. The glutathione adduct reacted readily with cysteine forming S-(N-methylcarbamoyl)cysteine. S-(N-methylcarbamoyl)cysteine and S-(N-methylcarbamoyl)glutathione also seem to be able to take part in reversible transcarbamoylation

reactions with peptides and proteins (Pearson et al. 1991).

Hundley et al., 1993b

In a pharmacokinetic study in monkeys, a saturation of DMF metabolism was also observed. Animals were exposed by whole-body inhalation to DMF at 30, 100 and 500 ppm during 13 weeks (6 hours per day/ 5 days per week) whereby their DMF AUC values increased 19- to 37-fold in male and 35- to 54-fold in female monkeys as the inhalation concentrations increased 5-fold (100 to 500 ppm) (Hundley et al., 1993b). Estimated plasma half-lives ranged from 1 - 2 hours to 4 - 15 hours for DMF and its metabolites "NMF", respectively. DMF was rapidly converted to "NMF" following 30 ppm exposures, with "NMF" plasma concentrations higher than DMF plasma concentrations at the 0.5 h timepoint. DMF-OH was always the main urinary metabolite (56 to 95 percent) regardless of exposure level or time on study.

Threadgill et al., 1987; Mráz and Turecek, 1987; Mráz et al. (1989; 1991; 1993)

In a study, in the urine of a test person exposed to DMF and N-methylformamide (NMF) the adduct N-acetal-S-(N-methyl-carbamoyl)cysteine resulting from the glutathione decomposition was found (Mráz and Turecek, 1987). The formation of this metabolite is a result of the second biotransformation pathway of DMF, whereby a carbamoylating species (possibly methyl isocyanate (WHO, 2001; Mráz et al., 1989)) reacts with glutathione (Threadgill et al., 1987). In turn, the formed glutathione- and its sequel adducts (S-methylcarbamoylcystein and the corresponding mercapturic acid) are responsible for cytotoxic effects (e.g. on hepatocytes) (Mráz et al., 1989). The authors postulate a relatively higher proportion of this metabolite in humans (for more details see human data). However, as limiting point, it should be taken into account that different ways of administration between humans and mice make it difficult to compare the data of humans and animals (Mráz et al., 1989).

In another study, metabolism of DMF in humans and three species of rodents (mouse, rat, hamster) was compared in terms of N-acetal-S-(N-methylcarbamoyl)cysteine (AMCC) (Mráz et al., 1991). The animals were treated with DMF (in saline) by single i.p. injections (7, 50, 500 mg/kg bw), whereas humans were exposed to DMF vapours at 30 to 60 mg/L for 8 hours. Urine was collected and investigated. The results suggest that the metabolic pathway leading to AMCC is much more important in humans than in rodents. Therefore, the risk from exposure to DMF in humans appears to be higher than that estimated from toxicological experiments on laboratory animals.

In another study with rats, experiments were conducted to elucidate enzymatic details of the metabolism of DMF (Mráz et al., 1993). DMF-toxicity has been associated with its metabolism to S-(N-methylcarbamoyl)glutathione (SMG) adduct. Major urinary metabolite was HMMF which undergoes oxidation in the formyl moiety, possibly via the intermediacy of its hydrolysis product N-methylformamide (NMF), and the reactive intermediate generated reacts with glutathione to yield SMG. Further, it was determined that the affinity of DMF for the metabolizing enzyme (cytochrome P 450 2E1) in rat liver microsomes is considerably higher than that of MMF or of HMMF. The respective values observed with human microsomes were very similar. With deuterated isotopomers investigations were performed on the kinetic deuterium isotope effect (KDIE) on DMF metabolism that was determined by incubations with rat microsomes in three ways. It could be shown that DMF inhibited the oxidation of MMF of HMMF to SMG. DMF competed with the P450 2E1 substrate MMF for the enzyme active site. The results obtained suggest that a) hepatic P 450 2E1 is an important catalyst of the metabolism of DMF, b) DMF inhibits its own metabolic toxification and c) there is a marked KDIE on the metabolic oxidation of DMF. In an earlier study, Lundberg et al. detected also that MMF concentrations 0 and 3 h after the end of the exposure of rats to the highest dose (2250 ppm) were generally lower than the concentrations at the same time after the low exposure (565 ppm) (1983). These results suggest that DMF biotransformation is delayed after the high exposure.

Greim et al., 1992

In a metabolism study, rats were administered DMF via oral, dermal and inhalation routes of

exposure. DMF was readily absorbed via all exposure routes and uniformly distributed throughout the organism. Metabolization took place mainly in the liver by microsomal enzymes. N-hydroxymethyl-N-methylformamide (DMF-OH or HMMF) was the main metabolite of DMF in animals and human beings and it is excreted with the urine. Mono-N-methylformamide (MMF) which was once considered to be the main metabolite of DMF was found only in low levels in the urine. It could be shown that MMF was mainly an artifact formed on the gas chromatographic column. Moreover it was shown, that intermediary metabolism produces to a lower extent via a second pathway glutathione adducts and its degradation products. As carbamoylating species, which reacts with glutathione methyl isocyanate was postulated but not proven. Moreover, investigations in animals had shown that at least after administration in single high doses, DMF can inhibit its own metabolism (saturated metabolism). Metabolic interaction occurs between DMF and ethanol. Ethanol and probably the ethanol metabolite, acetaldehyde inhibit the breakdown of N,N-dimethylformamide. Conversely, N,N-dimethylformamide inhibits the metabolism of ethanol and acetaldehyde. Thus, increased DMF levels in the blood were found after the administration of alcohol and increased alcohol or acetaldehyde levels for up to 24 hours were reported after exposure to N,N-dimethylformamide.

Filser et al., 1994

Steady state exposures of rats to DMF vapour at different concentrations were performed to obtain a quantitative relation between concentrations of DMF in atmosphere and concentrations of SMG in blood plasma. Dermal and inhalation uptake rates of DMF vapours were determined using systems for head-only and body-only exposures. N,N-dimethylformamide and N-methylcarbamoyl thioesters ("SMG") formed from DMF were investigated. A linear correlation between the concentration of DMF vapour up to 84 ppm and the concentration of SMG in blood plasma occurred in rats exposed at steady state to DMF. Toxic effects were in the range of 25 and 84 ppm DMF vapour. In details, At 25 ppm the steady state levels for "SMGs" (~ 50 µmol/L) was obtained after 12 hours of exposure and stayed in that range during a continuing exposure up to 48 hours. After exposure termination the "SMGs" were excreted with a half-life of approximately 2.8 hours. At 84 ppm the steady state "SMG" level was ~ 200 µmol/L; excretion half-life was ~ 2.2 hours. At 213 ppm, however, no "SMGs" were found until 6 hours following a 72 hours exposure time, presumably because of the inhibition of biotransformation.

B.5.1.2. Human information

Human volunteer data on toxicokinetics

Summaries of toxicokinetics study results in volunteers and in occupationally exposed workers are presented below.

Yonemoto and Suzuki, 1980

Urinary metabolite methylformamide (MF) was measured in nine workers exposed to DMF during handling surface-treating agents containing DMF for 5 consecutive days. The amount of urinary MF correlated well with the exposure to DMF. The time-weighted average individual measurement of DMF exposure during the morning and afternoon for 5 days differed by subjects and ranged from 0 to 5.13 ppm. The amount of daily MF excretion ranged from 0.4 to 19.56 mg. The excretion rate (mg/h) of MF usually started to increase by the beginning of exposure and peaked in the urine sample collected either at 20:00 h or at bedtime. The rate constant for MF excretion was estimated as 0.16/h. The difference between MF excretion rates obtained at bedtime and the hour of rising was statistically significant in the case of the group which had consumed no alcohol, whereas it was not in the case of the group which had been drinking. Alcohol consumption seems to be of particular significance in the metabolism of DMF.

Mráz et al., 1989

Ten volunteers who absorbed between 28 and 60 µmol/kg DMF during 8-hour exposure DMF in the air at 60 mg/m³ excreted in the urine within 72 hr between 16.1 and 48.7 % of the dose as N-hydroxymethyl)-N-methylformamide (HMMF), between 8.3 and 23.9 % as formamide, and between 9.7 and 22.8 % as N-acetyl-S-(N-methylcarbamoyl)cysteine (AMCC). AMCC together with HMMF, was also detected in the urine of workers after occupational exposure to DMF. In contrast, the portion of the dose (0.1, 0.7, or 7.0 mmol/kg given i.p.) which was metabolized in mice, rats, or hamsters to HMMF varied between 8.4 and 47.3 % of the dose; between 7.9 and 37.5 % were excreted as formamide and only between 1.1 and 5.2 %, as AMCC. The results suggest that there is a quantitative difference between the metabolic pathway of DMF to AMCC in humans and rodents. The authors' postulate a relatively higher proportion of AMCC in humans and suppose that the hepatotoxic potential of DMF in humans may be linked to this metabolite. Further, they suppose that rodents are less sensitive to DMF-induced hepatotoxicity due to their poor ability to metabolize DMF via this route. However, as limiting point, it should be taken into account that different ways of administration between humans and mice make it difficult to compare the data of humans and animals.

Mráz and Nohova, 1992b

Excretion of N,N-dimethylformamide (DMF) and DMF metabolites N-hydroxymethyl-N-methylformamide ("MF"), (N-hydroxymethylformamide) ("F") and (N-acetyl-S- (N-methyl-carbamoyl)cysteine) (AMCC) has been monitored in the urine of volunteers during and after their 8 -h exposure to DMF vapour at a concentration of 10, 30 and 60 mg/m³. The pulmonary ventilation in these experiments was typically about 10 L/min and the retention in the respiratory tract was 90 %. After exposure to 30 mg/m³ of DMF, the yield of compound determined in the urine represented 0.3 % (DMF), 22.3 % ("MF"), 13.2 % ("F") and 13.4 % (AMCC) of the dose absorbed via the respiratory tract (Table B12).

Table B12. Mass balance of DMF after 8 -h human exposure to DMF vapour

DMF conc.in air (mg/m³)	No. of persons	Pulmonary ventilation (L/min)	Total inhaled* (µmol)	Relative amounts excreted in urine during 120 h(%)			
				DMF	"MF"	"F"	"AMCC"
10	4ˆ	10.5 ± 0.8	635 ± 46	-	17.0 ± 3.0	-	13.7 ± 2.0
30	9ˆ	9.6 ± 1.4	1720 ± 260	0.3 ± 0.2	22.3 ± 5.8	13.2 ± 2.4	13.4 ± 2.3
60	9ˆ	10.1 ± 1.8	3545 ± 695	0.7 ± 0.4	23.6 ± 3.0	13.3 ± 3.6	13.7 ± 2.0

ˆ Data for one of the ten volunteers were excluded due to his atypically low pulmonary ventilation
* Calculated as a multiple of DMF concentration in the air, pulmonary ventilation for 8h and the retention in the respiratory tract (90 %).

Only a small, dose-dependent part of the absorbed DMF appeared unchanged in the urine (Table B12). According to the authors, DMF concentration in the urine is considered to be a better index of DMF uptake than the excretion rates. The actual metabolic yields of the given metabolites are somewhat lower than those shown in the Table B12 because of the contribution of the percutaneously absorbed DMF vapour to the total DMF intake. Under the conditions used, the amount absorbed through the skin accounted for about 20 % of the excreted metabolites.

The excretion curves of the particular compound attained their maximum 6-8h (DMF), 6 -8h ("MF"), 8 -14h ("F") and 24 -34h (AMCC) after the start of exposure. The half-times of excretion were approximately 2, 4, 7 and 23 h for DMF (not shown in the table), "MF", "F" and "AMCC", respectively (see table B16).

Table B13. Half-time of elimination of DMF metabolites after 8-h inhalation exposure to DMF vapour (calculated by least squares regression analysis of the linearized falling parts of the excretion curves of "MF", "F" and AMCC in intervals 10-26 h, 14-38 h and 38-72 h, respectively, after the beginning of the exposure to DMF).

DMF concentration in air (mg/m³)	No. of persons	Half-time of elimination (h)		
		"MF"	"F"	"AMCC"
10	4	4.0 ± 0.4	-	29.8 ± 4.0
30	10	3.8 ± 0.4	6.9 ± 0.7	23.1 ± 3.2
60	10	3.7 ± 0.5	7.2 ± 1.1	23.4 ± 2.8

In contrast to slow elimination of AMCC after exposure to DMF, AMCC was eliminated rapidly after AMCC intake. This discrepancy could be explained by rate-limiting reversible protein binding of a reactive metabolic intermediate of DMF, possibly methylisocyanate.

Käfferlein et al., 2005

In 35 healthy workers employed in the polyacrylic fiber industry, N-methylformamide (NMF) and N-acetyl-S-(N-methylcarbamoyl)cysteine (AMCC) in urine, and N-methylcarbamoylated haemoglobin (NMHb) in blood were measured. Workplace documentation and questionnaire information were used to categorise workers in groups exposed to low, medium, and high concentrations of DMF. All three biomarkers can be used to identify occupational exposure to DMF. However, only the analysis of NMHb could accurately distinguish between workers exposed to different concentrations of DMF. The median concentrations were determined to be 55.1, 122.8, and 152.6 nmol/g globin in workers exposed to low, medium, and high concentrations of DMF, respectively. It was possible by the use of NMHb to identify all working tasks with increased exposure to DMF. While fiber crimpers were found to be least exposed to DMF, persons washing, dyeing, or towing the fibers were found to be highly exposed to DMF. In addition, NMHb measurements were capable of uncovering working tasks, which previously were not associated with increased exposure to DMF; for example, the person preparing the fiber forming solution.

Cai et al., 1992

A factory survey was conducted in a plant where N,N-dimethylformamide (DMF) was in use during the production of polyurethane plastics and related materials. In all, 318 DMF-exposed workers (195 men and 123 women) and 143 non-exposed controls (67 men and 76 women) were examined for time-weighted average exposure (to DMF and other solvents by diffusive sampling), hematology, serum biochemistry, subjective symptoms, and clinical signs. Intensity of exposure to DMF: up to 7-9 ppm in workshop 1, about 3 ppm in workshop 2, and less than 1 ppm in workshops 3-5. Most of the exposed workers were exposed only to DMF, whereas others were exposed to a combination of DMF and toluene DMF exposure in the former group was up to 7.0 ppm (geometric mean on a workshop basis), whereas it was up to 2.1 ppm in combination with 4.2 ppm toluene. Both hematology and serum biochemistry, results (including aspartate and alanine aminotransferases, y-glutamyl transpeptidase and amylase) were essentially comparable among the 3 groups. There was, however, a dose-dependent increase in subjective symptoms, especially during work, and in digestive system-related symptoms such as nausea and abdominal pain in the past 3-month period. The prevalence rate of alcohol intolerance complaints among male (assumedly) social drinkers was also elevated in relation to DMF dose".

Greim et al., 1992

N-hydroxymethyl-N-methylformamide was the main metabolite of N,N-dimethylformamide in human beings and it is excreted with the urine. The cysteine adduct N-acetyl-S-(N-methylcarbamoyl)cysteine was found in urine at levels at 10 % to 23 % of the dose in persons who had inhaled DMF. Formation and excretion of the cysteine adduct (N-acetyl-S-(N-methylcarbamoyl)cysteine) in the urine of persons inhaling N,N-dimethylformamide takes place with a half-time of 23 hours. Metabolic

interaction occurs between N,N-dimethylformamide and ethanol. Ethanol and probably the ethanol metabolite, acetaldehyde inhibit the breakdown of N,N-dimethylformamide. Conversely, N,N-dimethylformamide inhibits the metabolism of ethanol and acetaldehyde. Thus, increased N,N-dimethylformamide levels in the blood were found after the administration of alcohol and increased alcohol or acetaldehyde levels for up to 24 hours were reported after exposure to N,N-dimethylformamide.

Wrbitzky and Angerer, 1998

DMF air monitoring and biological monitoring of the DMF metabolite NMF in urine of workers were carried out using instrumental analytical methods. DMF concentrations measured in the air ranged between <0.1 and 37.9 ppm (median 1.2 ppm). Diffusion tubes were used to collect personal air samples from workers exposed to DMF for 8 h. Before and after 8 h the concentration of metabolite NMF was determined for the internal exposure to DMF. Before the working phase of 8 h the NMF in urine was found to be 0.05 - 22 mg/L. After the working day 0.86 - 100 mg/L NMF was detected in the urine. The creatinine related values: (0.02-44.6 mg/g preshift; 0.4-62.3 postshift) (Table B14).

Table B14. External and internal exposure to DMF

	DMF air (ppm)	NMF urine (mg/L) preshift	NMF urine (mg/g creatinine) preshift	NMF urine (mg/L) postshift	NMF urine (mg/g creatinine) postshift
Range	<0.1-37.9	0.05-22.0	0.02-44.6	0.86-100.0	0.4-62.3

As shown in Table B15, it was found, as expected, that protective clothing worn as a result of the particular activities correlated significantly with higher DMF concentrations in the air. Despite the use of protective clothing, however, higher levels of internal exposure were found, as expected, by consideration of the individual ambient air concentrations.

Table B15. External and internal exposure according to personal protective measures

	Breathing mask		P	Protective gloves		P
	Yes	No		Yes	No	
DMF in air (ppm)	0.1-37.9	<0.1-13.9	<0.001	<0.1-37.9	<0.1-16.4	<0.001
NMF urine	2.6-62.3	0.4-42.7	<0.001	1.5-62.3	0.4-6.1	<0.001

The positive but relatively weak association observed between the DMF concentrations measured in the workplace air and the values recorded for internal exposure in this study can be explained by influencing factors such as dermal absorption or protective clothing. The results of the investigations indicate that dermal absorption has a great influence on the level of internal exposure. Particularly, in the 24 cases where the BAT value was exceeded without the SCOEL value (German MAK) being exceeded at the same time, increased dermal absorption must be regarded as the cause. Due to DMF's good dermal absorption and its irritative effects on the skin and mucous membranes, a complete skin status was determined for all persons. Evaluation of the exposure conditions and internal exposure of the employees (n =27) who currently suffered from a skin disease showed that despite their average exposure to DMF, the median value of 16.1 mg NMF/g creatinine recorded for those with eczema (n=7) was higher than that noted for those with healthy skin (5.0 mg NMF/g creatinine). Considering the small number of cases, this can only be an indication that in persons with eczema the skin barrier against hazardous substances is impaired. Interindividual differences in internal exposure were found for the specific work areas. The German BAT value (15 mg NMF/L urine) was exceeded in 36 persons (29 %) despite the use of breathing protection and protective gloves, without increased values being measured in the air. Additional investigation of a subcollective (n = 31) over a period of 4 days showed that NMF did not accumulate in the organism.

Dermal absorption

Percutaneous absorption of liquid and vapour N, N-dimethylformamide was shown in human volunteers (Mráz and Nohova, 1992). The volunteers were exposed to DMF vapours via the skin and inhaled fresh air via a mask. Dermal resorption rates accelerated after 4 -hour dermal exposure of volunteers to 51 mg DMF/m³ in an exposure room. The resorption rates correlated positively with increased temperature and humidity and accounted for 13 % - 36 % of totally excreted N-hydroxymethyl-N-methylformamide (NMF). Thus, increased humidity from 50 % to 100 % as well as increased temperature from 21 °C to 30 °C enhanced percutaneous penetration on volunteers exposed to DMF more than 3.5 times. As evidence for this, the excretion rates of NMF, the main metabolite of DMF, in urine during 24 hours were: at 21 °C and 50 % humidity 27 µmol, at 28 °C and 70 % humidity 44 µmol and at 30 °C and 100 % humidity 95 µmol. However, when volunteers were exposed to 51 mg/m³ both via inhalative and dermal way, the amount of NMF was 219 µmol. In another experiment, the volunteers were exposed to DMF by dipping hands up to the wrist in DMF for 2-20 min. Liquid DMF was resorbed with 9.4 ± 4.0 mg/cm² x h. After 15 min dipping of the hand in DMF, 930 µmol NMF, 606 µmol N-hydroxymethylformamide (F) and 597 µmol N-acetyl-S-(N-methylcarbamoyl) cysteine (AMCC) have been measured in urine of volunteers during 5 days. Half-time of excretion was 7.8 hours for NMF, 9.9 hours for F and 23.9 hours for AMCC. The amount of metabolites found was as high as that seen after 8-hour inhalation exposure to DMF vapour of 60 mg/m³. Furthermore, the relative composition of total urinary metabolites excreted after use of either the percutaneous or the inhalation route was very similar. However, the excretion half times after inhalation exposure were shorter: 4 hours for NMF and 6.9 hours for F. The excretion kinetics of AMCC were unaffected by the route of administration of DMF. In a patch experiment, DMF (2 mmol) was applied to the skin for 8 hours (Mráz and Nohova, 1992). 7.6 % of the absorbed DMF by the first four volunteers and 8.7 % by the second four volunteers were excreted as NMF during 24 hours, while the corresponding value for the same DMF dose absorbed through the lungs estimated as 16 % - 18 %.

Nomiyama et al. exposed thirteen healthy male volunteers to DMF vapour twice, via both skin and lungs for 4 hours at 27 °C and 44 % humidity (Nomiyama et al., 2001). The volunteers inhaled DMF of 7.1 ± 1.0 mL/m³ by a respirator connected to the chamber. In another experiment, the volunteers were exposed to DMF via the skin in a whole-body type exposure. Dermal exposure level was 6.2 ± 1.0 mL/m³. The excretion of NMF was 3.25 mg in urine after dermal application and 3.93 mg after inhalation exposure. Here from, DMF absorption via the skin and the lung were estimated to be 40.4 and 59.6 %, respectively. The biological half-time of urinary NMF after dermal exposure, 4.75 ± 1.63 h, was longer than that after respiratory exposure, 2.42 ± 0.63 h.

In another study with human volunteers, Chang et al. determined the unit increment of dermal exposure on total body burden of two biomarkers in urine: N-methylformamide (NMF) and non-metabolized DMF in 75 directly exposed workers to airborne DMF under typical for a factory exposure scenario(Chang et al., 2004). The study subjects wore no gloves. The respiratory exposure to DMF was determined by breathing –zone sampling for a full-work shift and dermal exposure was assessed by an adhesive patch-test method. The average airborne DMF concentrations collected in the working environment were 1.51 (4.81) ppm. Dermal exposure on hands were greater than those on forearms and accounted for 0.04 (4.61) and 0.03 (5.98) µg/cm² for hands and forearms, respectively. Using multiple linear regression, the net contribution of per unit increment of hands' exposure (µg/cm²) and airborne DMF exposure (ppm) to NMF were calculated to be 0.53 and 0.68 mg/L, respectively (Table B16). To urinary DMF, they were 0.46 and 0.73 mg/L for per unit increment of hands' exposure (µg/cm²) and airborne DMF exposure (ppm), respectively.

Table B16. Contribution of hand and airborne exposures into the increment of urinary biomarkers

Exposure description	Urinary biomarkers (mg/L)	
	U-NMF	U-DMF
Airborn exposure	0.68	0.73

Dermal exposure (hand)	0.53	0.46
DMF Exposure occupational (ppm (mg/cm²)	1.51 (4.81)	

The results of the study demonstrate that dermal exposure was significantly associated with urinary metabolites and represents 43.8 % and 38.6 % of NMF and non-metabolized DMF, respectively of totally excreted amounts of these metabolites.

From these data is clear that dermal exposure to DMF has a significant impact on the total systemic burden of DMF. In an *in vitro* test, Wang et al. confirmed this fact, determining skin permeability's of neat DMF and its mixtures with water. The penetration fluxes were the highest by neat DMF. 85.9 % of applied dose was still remaining in the skin surface, 4.98 % was still remaining in the skin layer, and 9.09 % penetrated through the skin layer after the 24-hour exposure. The DMF water mixtures penetrated slowly through the skin (Wang et al., 2009). The half-life of DMF retaining in the skin layer were 12.3, 4.07 and 1.24 h for 100 %-DMF, 50 %-DMF and 10 %-DMF, respectively. The estimated reservoir effect for neat DMF (34.1 %) was the highest than those of water mixtures. The test demonstrates that dermal exposure could prolong the internal burden even the external exposure of DMF is terminated.

Alcohol intolerance related to DMF exposure

Lyle and coworkers (1979) found facial flushing and other symptoms in 19 of a group of 102 men who worked with dimethylformamide (DMF). Twenty-six of the 34 episodes occurred after the workers had consumed alcoholic drinks. The symptoms included abdominal pain, flushing of skin on face, and arms, reddening of eyes, stomach ache, nausea etc. The flushing symptoms occurred at airborne DMF concentrations of 20 ppm. The highest recorded concentration of DMF in air was 200 ppm. The metabolite N-methylformamide (MF) was detected in the urine on 45 occasions, the highest recorded concentration being 77 µL/L. The authors attributed the DMF-ethanol reaction to the inhibition of acetaldehyde metabolism, probably by MF. Usually, the effects of alcohol intolerance persisted for several hours after working shift. However, there is single case noted, by a patient whose flushing symptoms persisted for many months after exposure ended (Cox and Mustchin, 1969). Lauwerys et al. studied workers exposed to DMF in an acrylic factory for the presence of biological signs of liver dysfunction and the NMF-concentration (pre- and post-shift), respectively (Lauwerys et al., 1980). The average DMF concentrations measured were in the range between 1.3 and 46.6 mg/m³ (median 13 mg/m³). NMF in urine samples collected at the end of the work shift did not exceed 40-50 mg/g creatinine. This level indicates an exposure which was reported as "safe" with regard to the acute and long term action of liver function. Serum liver enzymes (transaminases, OCT, 7-GT, AP) and bilirubin measurement were not different from those made in the control group. Nevertheless, some workers reported experiences of alcohol intolerance at the end of the day when they had been exposed to peak concentrations of DMF vapour. Similar findings were observed by Yonemoto et al. (Yonemoto et al., 1980). The cases of alcohol intolerance were reported in workers exposed for 3 years to 1-5 ppm DMF, although no increase in GOT, GPT, 7-GT was demonstrated. The amount of daily NMF excretion ranged from 0.4 to 19.56 mg. However, NMF excretion was delayed in workers with alcohol consumption. Cai et al. (Cai et al., 1992) reported that in workers exposed to max. 7 ppm DMF, the levels of liver function indicators were similar to controls, but subjective symptoms increased in a dose-dependent manner and the prevalence rate of alcohol intolerance complaints was elevated especially in workers with alcohol consumption. Authors suggested that a level at which no alcohol intolerance would occur is below that causing liver damage (Lauwerys et al., 1980, Yonemoto et al., 1980). In more recent studies (Wrbitzky and Angerer, 1998, Wrbitzky, 1999), a synergistic effect of alcohol consumption and increased liver indices was confirmed. Wrbitzky and Angerer found that exposure even to 22.2 ± 31 mg/m³ (7.3 ± 10.2 mL/m³) DMF in the air (corresponding to 16 ± 16 mg NMF/g creatinine) did not produce increased liver enzyme values in workers. It applies only to workers without alcohol consumption. In opposite to this, in workers with alcohol consumption, the liver indices were increased already at 1.4 mL/m³ (4.2 mg/m³), the value below SCOEL value of 15 mg/m³. Flush symptoms reported by these workers occurred in 71.5 % of persons compared to only 3.8 % in control persons. The effects of DMF and those of alcohol on liver values were dose-dependent. Furthermore, Wrbitzky using variance analysis showed that though alcohol

consumption together with DMF exposure yields to a pronounced Influence at liver indices, DMF alone possesses a minor influence (Wrbitzky, 1999). An additional examination of urine samples of 17 workers at the end of working day revealed that no alcohol intolerance symptoms were reported at average NMF concentrations in urine of 19 ± 24.9 mg NMF/L urine (range 1.07 - 99.96 mg NMF/L) (Angerer and Drexler, 2005; reported in MAK, 40. Lieferung, 2006). This range of metabolite NMF in urine corresponds to about 0.4 - 62.3 mg/g creatinine, reported by Wrbitzky and Angerer, the values at which pronounced complaints after alcohol consumption were reported. Such discrepancies could be related to a complex of factors such as level of exposure resulted both from inhalation and dermal exposure, individual susceptibility and amount of alcohol intake.

Conclusions

Absorption

When N-N-dimethylformamide (DMF) is administered *in vivo* orally, via inhalation or via skin, it is readily absorbed in animals and in humans (Käfferlein et al., 2005; Wrbitzky and Angerer, 1998; Filser et al., 1994; Hundley et al., 1993a, Greim et al., 1992, Mráz and Nohova, 1992). In humans, inhalation is the most relevant exposure route for DMF (Chang et al., 2004). A linear correlation was observed between the concentration of DMF vapour and concentrations of DMF in blood plasma of rats treated by inhalation and in humans after 8-hour working shift (Filser et al., 1994; Wrbitzky and Angerer, 1998; Chang et al., 2004). Besides this, dermal exposure provides a substantial contribution to the total body burden of DMF in exposed workers (Chang et al., 2004). DMF can be well absorbed via direct contact with the skin and via vapour. Skin absorption of the liquid DMF contributes to occupational exposure more than penetration of the DMF vapour (Mráz and Nohova, 1992). Percutaneous absorption of DMF vapour correlates positively with the increase of temperature and humidity and amounted to 13 % - 36 % (Mráz and Nohova, 1992) and 40.4 % (Nomiyama et al., 2001) of totally excreted NMF.

Distribution

DMF concentrations as well as its biotransformation product monomethylformamide (MMF) were measured in blood and other tissues of rats exposed to vapours of DMF (Lundberg et al., 1983). Both DMF and MMF were distributed fairly uniformly over the different tissues, though blood and kidneys usually had the highest concentrations. In a study with rats exposed by inhalation to DMF (labelled) vapours, statistically significant increases in the labeling index of lung were observed lungs. Therefore, an assumption was made that the lungs might also be a potential target organ of DMF exposure (DuPont Co., 1990). No effects were observed in rat liver, prostate, and nasal tissues (DuPont Co., 1990).

Metabolism

The metabolism of DMF occurs in the liver (Greim et al., 1992) via two main pathways, with one leading to the formation of N-(hydroxymethyl)-N-methylformamide (DMF-OH or HMMF) (DuPont Co., 1990; Greim et al., 1992; Mráz et al., 1993; Hundley et al., 1993). The other main pathway of metabolism leads to N-methylformamide (MMF or NMF), which can react with glutathione to S-(N-methylcarbamoyl) glutathione (SMG); this substance is a reactive intermediate (Mráz et al., 1993; Filser et al., 1994). Additionally, DMF can be bioactivated to methyl isocyanate, a reactive species associated with hepatotoxicity (Greim et al. 1992). It seems that hepatic P 450 2E1 is an important catalyst of the metabolism of DMF (Mráz et al., 1993).

HMMF was the main metabolite of N,N-dimethylformamide in animals while MMF was found only at low levels in the urine (Greim et al., 1992). It could also be shown that MMF, which was once considered to be the main metabolite of N,N-dimethylformamide, was mainly an artifact formed on the gas chromatographic column.

At high exposures, biotransformation of DMF was delayed in rats and monkeys (Mráz et al., 1993; Hundley et al., 1993). A quantitative difference between the metabolic pathway of DMF to AMCC in humans and rodents was also observed (Mráz et al., 1989). A relatively higher proportion of AMCC

was determined in humans comparing to animals supposing that the hepatotoxic potential of DMF in humans may be linked to this metabolite. Further, they supposed that rodents are less sensitive to DMF-induced hepatotoxicity due to their poor ability to metabolize DMF via this route. The glutathione- and its sequel adducts (S-methylcarbamoylcystein and the corresponding mercapturic acid S-methylcarbamoyl-N-acetyl-cysteine) appeared to be responsible for developmental toxic effects in an *in vitro* assay (Klug et al., 1998, cited in OECD SIDS, 2004).

Alcohol intolerance symptoms were reported by workers exposed to DMF (Angerer and Drexler, 2005; Cai et al., 1992; Yonemoto et al., 1980; Lyle et al., 1979). Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Furthermore, ethanol induces cytochrome P450 2E1 which facilitates the initial hydroxylation of DMF. Thus, exposure to DMF can cause severe alcohol intolerance (Yonemoto and Suzuki, 1980; Eben and Kimmerle, 1983, cited in OECD SIDS Report for SIAM 13, 2004). Additionally, DMF can be bioactivated to methyl isocyanate, a reactive species associated with hepatoxicity.

Excretion

DMF-OH represented 90 % of the summed DMF, DMF-OH, and MMF excreted in the urine (DuPont Co., 1990). DMF-OH was always the main urinary metabolite (56 - 95 %) regardless of exposure levels or time on study with monkeys (Hundley et al., 1993b), rats (Mráz et al., 1993) and humans (Mráz and Nohova, 1992, Käfferlein et al., 2005). In humans, the elimination of DMF metabolites after exposure via the skin to DMF vapour is slower compared to inhalation exposure (Mráz and Nohova, 1992, Nomiyama et al., 2001). The same applies to the dermal exposure of liquid DMF. Thus, for DMF skin represents a compartment characterized by rapid absorption, extensive accumulation and slow elimination.

Concerning accumulation potential, the biological half-life of DMF is about 4 hours (Kimmerle and Eben, 1975 (cited in Wrbitzky and Angerer, 1998), Mráz and Nohova, 1992a). The majority of substance was eliminated within 24 hours (Lauwerys et al., 1980). NMF was detectable in the urine 4 hours after beginning of the exposure. DMF concentration in blood decreased rapidly and was no longer detectable 4 hours after exposure. Urine analysis also showed that during repeated exposure to DMF, no accumulation of NMF occurred in the body. No accumulation was detected in humans during the 4 days of the investigation of the concentrations of NMF if concentrations of DMF were between 0.1 and 37.9 ppm (median 1.2 ppm) (Wrbitzky and Angerer, 1998). For AMCC, however, accumulation is described (Mráz and Nohova, 1992 a). After repeated inhalative exposure to 30 mg/m³ DMF, persons excreted the mercapturic acid at levels of ~13 % of the dose absorbed via respiratory tract with a total half-life (i.e. DMF biotransformation and excretion) of 23 hours (Mráz and Nohova, 1992).

A brief overview of ADME studies is presented in the following table.

Table B17. Overview of key toxicokinetics and dermal absorption studies

Species/ strain	Type study	Study design	Results (Absorption rates, metabolites)	Reference
Rats, Humans	Metabolism	Rats were administered via oral, dermal and inhalation routes. Human: inhalation route	DMF is readily absorbed via all exposure routes. N-hydroxymethyl-N-methylformamide is the main metabolite, while mono-N-methylformamide was found only at low levels in the urine. DMF inhibits alcohol metabolism in humans	Greim et al., 1992
Rats, mice	Toxicokinetic study	Whole body inhalation to 10, 250 and 500 ppm (two	Data are indicative of saturation of DMF (between 250 and 500 ppm) metabolism. NMF plasma data also indicate saturation.	Hundley et al., 1993a; International

Species/ strain	Type study	Study design	Results (Absorption rates, metabolites)	Reference
		weeks)	The major pathways for DMF metabolism: 1. Formation of DMF-OH and excretion via the urine. 2. Conversion of the DMF to N-methylformamide (NMF) and subsequent metabolism of NMF to a variety of metabolites including cysteine conjugate. Distribution into the lungs	DuPont and Co., 1990
Monkeys	Toxicokinetic study	Whole body inhalation to 30, 100 and 500 ppm (13 weeks, 6-h/d, 5d/w))	Saturation of DMF metabolism: as concentrations increased from 100 to 500 ppm. DMF-OH is the main urinary metabolite. Half-life for DMF is 1-2 hours, for other "NMF" metabolites – 4-15 hours.	Hundley et al., 1993b
CBA/CA mice, male Wistar rats	Metabolism	i.p administration of radiolabelled N-methylformamide and DMF	N-hydroxymethyl-N-methylformamide was a major urinary metabolite. Dimethylamine and methylamine were minor metabolites. 2 metabolic pathways could be distinguished: hydroxylation of the-carbon of the N-alkyl group and oxidation of the formyl moiety. N-acetyl-S-(N-methyl-carbamoyl)cysteine (AMCC) was identified as a reactive species associated with hepatotoxicity.	Kestell et al., 1985; 1986 a,b, 1987; BASF AG, 1990
Rats (Sprague Dawley)	Metabolism	Bile cannulated administration of methyl isocyanate in DMSO	S-(N-methylcarbamoyl)glutathione (SMG), a chemically-reactive glutathione conjugate is identified. Further, the metabolite reacted with cysteine forming S-(N-methylcarbamoyl)cysteine (SMC). SMG and SMC reacted with peptides and proteins	Pearson et al., 1990, 1991
Human, mice, rats, hamsters	Metabolism	Inhalation exposure, i.p. injection in animals	N-acetal-S-(N-methylcarbamoyl)cysteine (AMCC) resulted from glutathione decomposition in humans. S-(N-Methylcarbamoyl)glutathione has been identified as biliary metabolite in mice. Metabolic pathway leading to AMCC is more important in humans. AMCC is related to hepatotoxicity. Hepatic P450 2E1 metabolizes DMF.	Threadgill et al., 1987; Mráz and Turecek, 1987; Mráz et al., 1989, 1991, 1993
Rats (Sprague Dawley)	Metabolism	Dermal and inhalation exposure to DMF vapours were determined using systems for head-only and body-only exposures.	Linear correlation between concentrations of SMG in blood and exposure concentrations of DMF up to 84 ppm was established.	Filser et al., 1994
Human	Absorption, Metabolism, Excretion	8-hour exposure to DMF conc. Of 10, 30, and 60 mg/m³	After exposure to 30 mg/m³: 0.3 % DMF, 22.3 % N-hydroxymethyl-N-methylformamide (MF), 13.2 % N-hydroxymethylformamide (F) and 13.4 % AMCC.	Mráz and Nohova, 1992a

Species/ strain	Type study	Study design	Results (Absorption rates, metabolites)	Reference
			20 % of metabolites were related to dermal absorption of DMF; Excretion maximum: 6-8 h (DMF), 6-8 h (MF), 8-14 h (F), 24-34 (AMCC).	
Human	Percutaneous absorption	Patch test, hand dipping (15 min) and inhalation exposure to 50 mg/m³. Absorption rates and metabolites determination	Liquid DMF was absorbed through the skin at a rate of 9.4 mg/cm² x 1hour. Percutaneous absorption of DMF vapour depended strongly on ambient temperature and humidity and accounted for 13 -36 % of totally excreted "MF". The yield of metabolites after transdermal DMF absorption was only half of that seen after pulmonary absorption. Elimination of "MF" and "F" but not of AMCC was delayed.	Mráz and Nohova, 1992b
Human	Biological monitoring	Inhalation to 0.1-37.9 ppm (median 1.2 ppm) DMF;	Positive correlation between air conc. of DMF and urinary metabolites concentrations. DMF and its metabolites do not accumulate in the organism. German BAT value of 15 mg NMF/L urine) was exceeded without SCOEL value (German MAK) being exceeded.	Wrbitzky and Angerer, 1998
Human	Volunteer study	Exposure to DMF dermally and via inhalation	DMF absorption via the skin and the lung were estimated to be 40.4 and 59.6 %, respectively. The half-life of dermal "NMF" was 4.75 ± 1.63 h longer than that after respiratory exposure, 2.42 ± 0.63 h.	Nomiyama et al., 2001
Human	Volunteer study (percutaneous absorption)	Exposure to DMF by inhalation without wearing gloves and patch test (24-hour)	Dermal exposure to DMF has a significant impact on total systemic burden.	Chang et al., 2004
porcine skin	*In vitro* skin penetration study	equivalent or similar to OECD Guideline 428 (Skin Absorption: *in Vitro* Method)	The penetration is the highest by neat DMF. After 24-hour exposure to the skin, 85.9 % was still in the skin surface, 4.98 % in the skin layer, and 9.09 % penetrated through the skin.	Wang et al., 2009

B.5.2. Acute toxicity

Information was obtained from the registration dossier and OECD SIDS (2004). DMF has a low acute toxicity by oral, dermal and inhalation routes. Oral LD_{50} > 3010 mg/kg bw was established in rats (BASF AG, 1972). Further studies in rats revealed LD_{50} values in the range between 2200 and 7550 mg/kg bw (BUA, 1991, cited in OECD SIDS, 2004). The substance is of low toxicity potential also via dermal and inhalation routes of exposure. In the key acute dermal toxicity study (TSCATS: OTS 0516779, 1978), LD_{50} > 3160 mg/kg bw/day was established for rats. Acute inhalation of the maximum technically attainable concentration of 5900 mg DMF/m³ by rats resulted in a LC_{50} value of > 5900 mg/m³/ 4 h; (BASF, 1979). Irregular or intermittent respiration was observed in the treated animals. The surviving animals recovered 6 -7 days after exposure. These animals did not show any gross lesions at necropsy while the animals that died during the study had some organ findings, e. g. discoloration of the liver, hemorrhage in thymus and punctate hemorrhage in pancreas and in the gastric mucous membrane.

Low toxicity was also observed after intraperitoneal (i.p.) and subcutaneous (s.c.) injection in rats and mice. LD_{50} values ranged from 1900 to 5035 mg/kg bw in rats and mice for i.p. route and from 1425 to 3800 mg/kg bw for s.c route in rats and mice.

Conclusion

The acute toxicity of DMF is low as was previously concluded in the OECD SIDS (2004).

B.5.3. Irritation

Information was obtained from the registration dossier and OECD SIDS (2004). DMF is not irritating to skin but irritating to eyes. In inhalation studies (acute and repeated), the substance did not cause respiratory tract irritation (BASF, 1979; Malley et al., 1994; Lynch et al., 2003)

In the skin irritation study (BASF AG, 1952), the neat substance (about 0.5 mL) was administered for 20 hours on the shaved back of 4 albino rabbits. After removal of the bandage only one animal showed faint redness which was disappeared on the second day. The other animals were without any findings. In the acute dermal study (TSCATS: OTS 0516779, 1978), the overall irritation score was 0 on day 2, 4, 8, 11, and 15 after 24-hour exposure of the undiluted substance to the intact and abraded skin of rats under occlusive conditions. Thus DMF was not regarded to be irritating to the skin of rabbits or rats.

In an eye irritation study, DMF of 50 µL (undiluted, 50 % and 10 % solution) was applied to the conjunctival sac of one eye in 3 animals (BASF AG, 1952). After 10 minutes, 1, 3 and 24 hours the eyes were examined and in case of findings, observation was continued until the findings disappeared. The eyes were not washed out after 24 hours as specified in OECD Guideline 405. Marked redness and chemosis as well as purulent secretion were observed in the animal treated with undiluted DMF. Besides this, transient opacity of the cornea occurred two days after substance application in this animal. The animal recovered and was without findings 6 days after treatment. The 50 % solution resulted in slight erythema and chemosis after 10 min, 1 hour and 3 hours post application. The animal recovered and was without findings 3 days after treatment. The 10 % solution generated slight erythema after 10 min, 1hour and 3 hour. The animal recovered and was without findings 24 h after treatment.

In another eye irritation study, instillation of 0.1 mL of neat test substance into one eye of 6 rabbits without rinsing resulted in large blisters on the inside of upper and lower lids at the 1 and 4 hour readings. Blisters decreased in size at the 24 hour reading and were disappeared at 48 hours (TSCATS: OTS 0516779, 1978). Primary irritation index was 50.8 after 1 h decreasing to 35.8 after 72 h and 35.0 on day 4 decreasing to 3.3 on day 13 (max. = 110). All findings were fully reversible within 14-day observation period.

Conclusion

DMF is not irritating to skin but irritating to eyes.

B.5.4. Corrosivity

DMF is not corrosive.

B.5.5. Sensitisation

Information was obtained from the registration dossier and OECD SIDS (2004).

DMF was used as a vehicle in a two-tiered LLNA that was under validation process (Ulrich et al., 2001). Groups of 6 female BALB/C strain mice (6 - 8 weeks old) were used. During tier I a wide range of concentrations of test chemical solutions or vehicle (volume: 25 µL) were applied on three consecutive days to the dorsum of both ears. Mice were killed 24 hours after the last application to determine ear and local lymph node weights and lymph node cell counts. Ear weights were

determined to correlate chemical induced skin irritation with the ear-draining lymph node activation potential. For comparison of the induction and challenge responses, mice were treated on the shaved back with 50 µL of test chemical or vehicle alone on three consecutive days (induction phase treatment). Then mice were challenged 12 days after the final induction phase exposure with 25 µL of test chemical or vehicle on the dorsum of both ears for a further 3 days (challenge phase treatment). Lymph nodes were excised 24 hours after the final challenge phase treatment. A tier II LLNA protocol was used to finally differentiate between true irritants and contact allergens. To investigate the impact of different vehicles on the primary response induced by two contact allergens, DMF and acetone/oil olive was used as one of such vehicles. Both contact allergens were compared either to the untreated control (aqua bidest) or to the corresponding vehicle control. Topical treatment of mice with the vehicle DMF led to slight ear-draining lymph node activation as expressed by increased weights and cell counts in comparison to the untreated animals. However, this observation was not reproducible in a second experiment (i.e. when DMF was tested as vehicle for eugenol and as vehicle alone in comparison to the respective untreated control group). N, N-dimethylformamide was also negative in Guinea Pig Maximization Test (Bainova, 1985).

Regarding respiratory sensitization, in the sub-chronic inhalation study (Lynch et al., 2003), the animals were exposed to DMF by whole body inhalation exposure at 0, 50, 100, 200, 400, or 800 ppm, 6h/day, 5days/week, for 13 weeks. DMF was mildly irritating to rats exposed at 400 and 800 ppm, evidenced by occasional nasal and ocular discharges. Organs and tissues from high dose group animals and from the controls were examined for gross lesions and histopathologically. Under these organs were also lungs, main stem bronchi and tracheas. Microscopically, no lesions, associated with sensitization response to DMF, were found in these organs. DMF was not sensitizing to the respiratory tract in the test animals.

Conclusion

DMF is not sensitizing to skin or respiratory tract.

B.5.6. Repeated dose toxicity

Information was obtained from the registration dossier and OECD SIDS (2004). The study descriptions and NOAELs /LOAELs were adopted in general, unless stated otherwise.

Oral

BASF, 1977

In a 28-day study, Sprague–Dawley rats received 250, 500, 1000 and 2000 µL N,N-dimethylformamide/
kg bw (about 238, 475, 950 and 1900 mg/kg bw/day) by gavage on 5 days/week. In the highest dose group all animals died, mostly at the beginning of the study. At 1000 µL/kg bw/day all animals were affected by reduced food consumption and reduced body weight, males already at the beginning, females at the end of the study. Hepatic injury was characterized by changes in clinical chemistry values, e.g. increased enzyme activities. Relative liver weights were increased in both sexes. Histological examination revealed an acute to subacute hemorrhagic liver dystrophy with necrosis in both sexes in the two high dose groups. Disturbances in kidney function were characterized by elevated urea (females) and creatinine values, the latter one in both sexes. Relative kidney weights were increased in the males. At 250 and 500 µL/kg bw/day reduced food consumption in the males and at 500 µL/kg bw/day reduced body weight was observed in the males. For the observation of increased relative liver weights in both sexes and of increased relative kidney weights in the males no histopathological correlate was found. NOAEL of 238 mg/kg bw/day and LOAEL of 475 mg/kg bw/day were established.

TSCATS: OTS 0520880, 1960; TSCATS: OTS 0571664, 1960; TSCATS: OTS 0572893, 1960

In a 90-day feeding study Charles River CD strain rats received 200, 1000 and 5000 ppm DMF (about 12, 60 and 300 mg/kg bw/day). Liver weight, mild liver injury as well changed blood picture were observed. Relative liver weights were slightly increased at 1000 ppm, a histopathological correlate was not found but hypercholesterolemia and elevated phospholipid values were observed in females at this dose level. Leucocytosis and a decrease in the red blood cell count were observed. At 5000 ppm both sexes showed depressed body weight gain and reduced food consumption. Slight anemia, leukocytosis, hypercholesterolemia and elevated phospholipid concentrations were seen. Increased relative liver weights together with mild liver injury in the histological examination were found in both sexes. Increased relative liver weights at 1000 and 5000 ppm were dose-related. In conclusion, the liver was the predominant organ of DMF toxicity. NOAEL of 200 ppm was established for male and female animals.

Elovaara et al., 1983

In a subacute study, male Wistar rats received DMF via drinking water for 2 weeks or 7 weeks. Upon evaluation of the effects in the liver increased values were found for the following parameters: liver/body weight-ratio, GSH content, ethoxycoumarin O-deethylase and UDP glucuronosyltransferase activities. The GSH content, deethylase activity and, transiently, the glucuronidation activity were slightly increased also in the kidneys. Oxidative N-demethylation of DMF by hepatic microsomes *in vitro* was not enhanced by oral treatment. No DMF-dependent formaldehyde liberation *in vitro* could be detected under conditions where formaldehyde liberation from N,N-dimethylnitrosamine could be demonstrated. However, the endogenous rate of formaldehyde generation by liver microsomes isolated from DMF-treated rats was enhanced with the highest oral dose of DMF. The daily intake of DMF lowered the activities of both formaldehyde and propionaldehyde dehydrogenases in the liver soluble fraction. No inhibition of these dehydrogenases was shown *in vitro* by DMF (510 mM) or by its main urinary metabolite N-methylformamide (510 mM). The observed impairment of aldehyde oxidation in liver and kidneys of the rat after the DMF intake could explain the mechanism behind the alcohol intolerance observed in man after DMF exposure.

Inhalation

Malley et al., 1994

In chronic inhalation studies Crl: CD BR rats were exposed over a period of 2 years and Crl: CD-1 (ICR) BR mice were exposed for 18 months at concentrations of 25, 100 and 400 ppm (about 80, 300 and 1210 mg/m³) 5 d/w and 6 h/d (Malley et al., 1994). In the rats body weight and body weight gain were reduced in both sexes at 400 ppm and in the male animals at 100 ppm. Moreover, the animals in these groups showed increased enzyme activity (serum sorbitol dehydrogenase, Table B18), increased liver weights (Table B18) and some histopathological findings in the liver (Table B18). There was no compound related increase of tumors. Estrous cycles were not altered in the females. Similar findings were observed in mice. At 400 ppm liver weights were increased in both sexes and at 100 ppm in the males. At all concentrations tested minimal to mild hepatocellular hypertrophy was observed (incidence being dose-related). Individual hepatocellular necrosis together with some other histopathological findings (minimal to moderate kupffer cell hyperplasia with pigment accumulation of lipofuscin and hemosiderin) were seen in all groups (also control, incidence being greater in DMF-treated animals). A compound-related increase in tumors was not observed and there was no effect on estrous cycles in female mice. According to the authors, a NOEC (no-observable-effect level) was not achieved in mice due to morphological changes seen in the liver at all three test concentrations; nevertheless they expected the NOEC to be close to 25 ppm due to the minimal changes observed at this concentration. These minimal changes included a slightly (for the males significantly) increased incidence of hepatocellular hypertrophy, dose-related and statistically significantly increased incidence of hepatic single cell necrosis in both sexes, and dose-related (for the males significantly) increased incidences of hepatic kupffer cell hyperplasia and pigment accumulation. For rats, **the NOEC is 25 ppm (80 mg/m³)** based on the body weight changes, clinical chemistry changes and hepatotoxic effects observed at 100 and 400 ppm. LOAEC was 100 ppm (300 mg/m³).

Table B18. Effect of DMF on Sorbitol Dehydrogenase Activity in Male and Female Rats[a].

	3 Months	6 Months	12 Months	18 Months	24 Months
Concentration (ppm)	**Males**				
0	7.0[b](3.3)	10.4 (7.5)	10.9 (4.8)	6.5 (2.1)	2.0 (0.9)
25	9.8 (5.5)	11.5 (6.1)	18.9 (17.6)	9.7 (3.3)	4.4 (2.3)*
100	35.0 (26.4)*	23.0 (17.9)	33.6 (33.1)*	19.8 (10.6)*	18.3 (24.3)*
400	22.6 (18.7)*	19.4 (10.8)	21.7 (12.5)*	19.3 (15.8)*	9.7 (8.1)*
Concentration (ppm)	**Females**				
0	11.5 (2.8)	20.9 (24.9)	6.6 (2.8)	6.0 (1.5)	5.7 (6.9)
25	11.0 (3.3)	7.7 (3.0)	7.6 (3.3)	14.8 (11.1)*	9.0 (11.0)
100	17.4 (6.0)*	18.4 (9.0)	17.3 (6.3)*	9.7 (4.3)*	4.9 (3.4)
400	30.9 (15.5)*	27.8 (18.0)	23.8 (13.0)*	23.2 (25.0)*	12.9 (13.7)

[a] 10 Rats/sex/concentration were sampled at each time point.

[b] Mean and standard deviation. Units are U/liter (U is 1 µmol/min where µmol refers to the amount of substrate converted).

* Statistically significant at $P < 0.05$.

Table B19. Effect of DMF on Relative[a] Liver Weight in Rats and Mice.

	DMF (ppm)			
	0	**25**	**100**	**400**
Male rats				
12 Months[b]	2.54 (0.18)	2.73 (0.34)	2.93* (0.32)	3.26* (0.31)
24 Months[c]	2.87 (0.45)	2.81 (0.35)	3.28 (0.53)	3.58* (0.73)
Female rats				
12 Months[b]	2.64 (0.24)	2.70 (0.41)	3.25* (0.40)	3.34* (0.40)
24 Months[c]	3.12 (0.67)	3.43 (1.06)	3.33 (0.71)	3.86* (0.61)
Male mice				
18 Months[d]	5.85 (1.18)	5.94 (1.45)	7.06* (2.04)	7.80* (2.35)
Female mice				
18 Months[d]	5.59 (0.92)	5.71 (0.95)	5.99 (1.45)	6.35* (0.78)

[a] % of body weight.

[b] Livers evaluated from 10 rats/sex/concentration.

[c] For males n = 17, 19, 21, and 26 livers evaluated for 0, 25, 100, and 400 ppm, respectively. For females n = 22, 14, 12, and 23 livers evaluated for 0, 25, 100, and 400 ppm, respectively.

[d] For males n = 31, 42, 38, and 36 livers evaluated for 0,25, 100, and 400 ppm, respectively. For females n = 42, 35, 36, and 47 livers evaluated for 0, 25, 100, and 400 ppm, respectively.

* Statistically significant at $P < 0.05$.

Table B20. Incidence (%) of Compound-Related Morphological Observations in Rats Exposed to DMF for 24 Months[a].

Lesion	**DMF (ppm)**			
	0	**25**	**100**	**400**
Centrilobular Hepatocellular Hypertrophy[b]				
Male	0	0	5*	30*
Female	0	0	3*	40*
Hepatic single cell necrosis[b]				
Male	2	2	3	30*
Female	0	0	5*	18*
Hepatic accumulation of lipofuscin/hemosiderin[b]				
Male	4	4	17*	58*
Female	8	7	22*	61*
Hepatic foci of alterations[b]				
Male: clear cell	11	8	22*	35*
Male: eosinophilic	33	36	24	45
Female: clear cell	5	5	14	24*
Female: eosinophilic	22	12	25	40*

[a] Data represent total percentage incidence for both unscheduled and scheduled deaths for the interval 12-24 months.

[b] The number of livers examined was 57, 59, 58, and 60 for 0, 25, 100, and 400 ppm males, respectively. For females exposed to 0, 25, 100, or 400 ppm, the number of livers examined was 60, 59, 59, and 62, respectively.

* Statistically significant at $P < 0.05$.

NTP 13-week studies, 1992 (Lynch et al., 2003)

Fischer 344 rats and B6C3F1 mice were exposed by whole-body exposure to DMF vapours at concentrations of 0, 50, 100, 200, 400 and 800 ppm 6 h/day, 5 days/week for 13 weeks. Rats were 51 days of age at the first exposure, they were subdivided into 3 study groups, 10 of each sex for each exposure level: a base study group, a cardiovascular group (blood pressure and electrocardiograms were determined) and a renal function (urinalysis) group. Mice were 46 days of age at the first exposure. Animals were observed twice daily for mortality and moribundity. Body weights were measured weekly and at necropsy. Moreover sperm morphology and vaginal cytology evaluations were performed on rats and on mice exposed to 0, 50, 200 and 800 ppm DMF. Epididymal sperm motility was evaluated at necropsy and vaginal cytology was done by vaginal lavage with saline during the 2 weeks just before necropsy. Clinical pathology investigations were performed on cardiovascular study rats at 4 and 23 days and on base-study rats at 13 weeks. Urinalysis was performed in 5 rats/sex in the 0, 50, 200 and 800 ppm groups. Kidney histology was performed on these animals. Blood pressure and electrocardiograms were measured within 24 hours of the last DMF exposure in the cardiovacular group rats. The animals were killed and the heart removed for microscopic examination. At study termination rats in the base study and the renal function groups as well as mice from all groups were killed and complete necropsies were performed. Examination for gross lesions was done and weights of liver, thymus, kidneys, testicles, heart and lungs were recorded. The target organ, i.e. the liver was microscopically examined in all dose groups of rats and mice and the following tissues were examined microscopically from all control and high dose group-animals from the base study group: adrenals, brain, epididymis, seminal vesicles, prostate, testes, ovaries, uterus, esophagus, eyes (if grossly abnormal), femur with marrow, gross lesions and tissue masses with regional lymph nodes, heart, aorta, intestines, kidneys, larynx, liver, lungs, lymph nodes, mammary gland with adjacent skin, nasal cavity and turbinales, pancreas, parathyroid glands, pharynx (if grossly abnormal), pituitary, preputial or clitoral glands, salivary glands, spleen, skeletal muscle, stomach, thymus, thyroid, trachea, urinary bladder and vagina.

In the rats, there was no substance-related mortality. Body weight gains were reduced by approx. 47-65 % in rats exposed to 800 ppm and to a lesser extent in the animals of the 400 ppm group (Table B21). Evidence for hepatocellular injury was seen as early as day 4 based on increases in activities of liver-specific enzymes (e.g. ALT, SDH and ICDH) in the serum of both sexes at 200-800 ppm DMF. Serum cholesterol levels were increased in all exposed rats at all time points (i.e. 4, 24 and 91 days) (Table B22 (males); Table B23(females). Relative liver weights were increased in the males at 100 ppm and above and at all concentrations in the females (Table B27). Minimal to moderate centrilobular hepatocellular necrosis was seen in both sexes at 400 and 800 ppm and pigment accumulation (hemosiderin and lipofuscin) in macrophages and kupffer cells was found in both sexes at the highest concentration (Table B21). Prolonged diestrus was observed in 7 of 10 females exposed at 800 ppm, i.e. at a concentration that produced hepatotoxicity and reduced body weight gain. Relative testis weights were increased at 400 and 800 ppm DMF, however, no microscopical findings or any adverse effects on sperm density or motility were observed. For male and female rats the no-observed-adverse effect concentration (NOAEC) for microscopic liver injury was 200 ppm.

Table B21. Survival and Weight Gain of F344/N Rats in the 13-week Inhalation Studies of N,N-Dimethylformamide.

Exposure concentration (ppm)	Survival[a]	Mean body weights			Final Weights relative to Controls (%) [d]
		Initial	Final[b]	Change[c]	
Males					
0	10/10	150.6	349.4	198.8	
50	10/10	160.3	353.0	192.7	101
100	10/10	151.2	342.8	191.6	98
200	10/10	157.2	358.5	201.3	103

400	10/10	154.0	330.7	176.7	95
800	10/10	163.5	268.8	105.3	77
Females					
0	10/10	118.6	193.0	74.4	
50	10/10	116.3	201.6	85.3	104
100	10/10	112.9	206.9	94.0	107
200	10/10	116.7	193.7	77.0	100
400	10/10	113.9	175.0	61.1	91
800	10/10	120.3	146.2	25.9	76

[a] Number surviving at 13 weeks/number of animals per dose group.
[b] At necropsy.
[c] Mean weight change of the animals in each dose group.
[d] (Dosed group mean/Control group mean) x 100.

Table B22. Selected Clinical Chemistry Results from Male Rats Exposed to Inhaled DMF for up to 13 Weeks ((Table 2 from Lynch et al., 2003).

ANALYTE (Units)	DMF concentrations (ppm)					
	0	50	100	200	400	800
SDH (IU/L)						
Day 4	20 ± 1[a]	19 ± 1	23 ± 2	28 ± 1**	43 ± 2**	130 ± 56**
Day 24	14 ± 1[b]	14 ± 1	24 ± 5**	33 ± 2**	55 ± 4**	251 ± 63**
Day 91	35 ± 4	41 ± 9	41 ± 3	70 ± 10**	94 ± 11**	227 ± 43**[b]
ALT (IU/L)						
Day 4	47 ± 1	45 ± 1	49 ± 2	53 ± 1*	74 ± 4**	356 ± 170**
Day 24	37 ± 1[b]	46 ± 3**	62 ±10**	69 ± 3**	123 ± 9**	420 ± 90**
Day 91	77 ± 7	75 ± 9	77 ± 6	102 ± 11	125 ± 13**	323 ± 48**
ICD (IU/L)						
Day 4	15.0 ± 2.3	11.5 ± 1.5	12.2 ± 2.4	12.7 ± 2.4	14.6 ± 1.7	32.9 ± 7.2*
Day 24	13.5 ± 2.2	13.8 ± 1.0	14.1 ± 2.7	14.5 ± 1.8	17.6 ± 2.1	78.8 ± 17.5**
Day 91	9.1 ± 2.9	7.7 ± 2.3	9.4 ± 2.2	9.3 ± 2.6	17.1 ± 7.1	19.3 ± 2.2**
CHOL (mg/dL)						
Day 4	75 ± 2[(b)]	97 ± 3**	112 ± 3**	112 ± 3**	116 ± 3**	109 ± 3**
Day 24	70 ± 1[(b)]	81 ± 2**[(b)]	82 ± 2**	84 ± 1**	81 ± 2**	91 ± 3**
Day 91	83 ± 3	94 ± 4*	102 ± 3**	98 ± 3**	98 ± 2**	134 ± 6**
TBA (µL/L)						
Day 4	11.4 ± 1.9	10.6 ± 0.9	15.1 ± 1.8	10.9 ± 1.4	19.2 ± 1.6**	36.8 ± 5.2**
Day 24	16.6 ± 2.12	17.3 ± 1.8	17.1 ± 1.1	16.7 ± 1.2	28.7 ± 4.3**	73.0 ± 16.3**
Day 91	8.4 ± 1.6	9.1 ± 1.7	12.1 ± 1.2	10.4 ± 1.1	14.7 ± 2.6*	48.2 ± 6.8**

[a]Mean ± SE; 10 animals/group except where indicated.
[b]n=9.
*Significantly different from control, $p < 0.05$.
**Significantly different from control, $p < 0.01$.

Table B23. Selected Clinical Chemistry Results from Female Rats Exposed to Inhaled DMF for up to 13 Weeks ((Table 3 from Lynch et al., 2003).

ANALYTE (UNITS)	DMF concentrations (ppm)					
	0	50	100	200	400	800
SDH (IU/L)						
Day 4	23 ± 0[a]	24 ± 1	23 ± 1	28 ± 1**	40 ± 3**	103 ± 24**
Day 24	21 ± 1	19 ± 1	22 ± 1	29 ± 2**	30 ± 2**	53 ± 5**[b]
Day 91	26 ± 2	26 ± 1	29 ± 2	40 ± 3**	48 ± 5**	171 ± 18**
ALT (IU/L)						
Day 4	42 ± 2	41 ± 1	40 ± 1	41 ± 1	46 ± 2	172 ± 39**
Day 24	32 ± 1	35 ± 2	36 ± 1*	38 ± 1**	44 ± 3**	98 ± 8**[b]
Day 91	54 ± 4	52 ± 3	60 ± 5	49 ± 2	66 ± 6	319 ± 31**[b]
ICD (IU/L)						
Day 4	11.9 ± 1.2	12.7 ± 2.1	12.2 ± 2.3	15.4 ± 3.5	13.5 ± 1.3	30.2 ± 5.4**
Day 24	7.5 ± 0.9	13.8 ± 3.0*	9.3 ± 1.7	11.3 ± 1.3*	11.1 ± 1.4	22.3 ± 2.6**[b]
Day 91	4.3 ± 0.7	6.9 ± 1.3	5.7 ± 0.7	10.1 ± 1.7**	5.7 ± 0.8*	66.4 ± 12.0**
CHOL (mg/L)						
Day 4	97 ± 2	120 ± 2**	137 ± 4**	152 ± 6**	141 ± 3**	138 ± 4**
Day 24	89 ± 2	106 ± 2**	106 ± 2**	117 ± 2**	111 ± 2**	117 ± 4**
Day 91	97 ± 3	109 ± 2**	129 ± 2**	115 ± 2**	137 ± 3**	136 ± 4**
TBA (µm/L)						
Day 4	15.0 ± 1.0	16.5 ± 2.2	16.0 ± 1.6	16.2 ± 0.8	18.7 ± 1.6	34.8 ± 4.3**
Day 24	9.6 ± 1.5	12.7 ± 1.9	11.6 ± 1.5	15.7 ± 2.0*	23.8 ± 3.7**	67.2 ± 13.2**
Day 91	8.5 ± 1.1	7.9 ± 1.5	13.9 ± 2.1	12.3 ± 2.1	27.6 ± 2.7**	37.5 ± 4.0**

[a]Mean ± SE; 10 animals/group except where indicated.
[b]n=9.
*Significantly different from control, $p < 0.05$.
**Significantly different from control, $p < 0.01$.

Table B24. Absolute and Relative Liver Weights in Rats Exposed to Inhaled DMF for 13 Weeks.

	DMF concentration (ppm)					
	0	50	100	200	400	800
Males						
Absolute	13.28 ± 0.43[a]	14.30 ± 0.40	15.16 ± 0.34**	16.62 ± 0.50**	14.98 ± 0.35*	10.79 ± 0.34**
Relative	3.80 ± 0.073[b]	4.05 ± 0.09*	4.43 ± 0.12**	4.63 ± 0.11**	4.53 ± 0.09**	4.02 ± 0.09**
Females						
Absolute	6.55 ± 0.17	7.50 ± 0.23**	8.17 ± 0.17**	7.41 ± 0.18*	7.07 ± 0.26	5.37 ± 0.12**
Relative	3.39 ± 0.07	3.72 ± 0.09**	3.95 ± 0.07**	3.83 ± 0.10**	4.04 ± 0.11**	3.68 ± 0.06**

[a]Mean ± SE (g); 10 animals/group.
[b]Organ weight/body weight X 100; mean of individual ratios.
*Significantly different from control, $p<0.05$.

**Significantly different from control, p<0.01.

Table B25. Incidence of Liver Lesions in Rats Exposed to Inhaled DMF for 13 Weeks.

	DMF concentration (ppm)					
	0	**50**	**100**	**200**	**400**	**800**
Males						
Hepatocyte necrosis	0/10	0/10	0/10	0/10	10/10** (1.0)a	10/10** (1.7)
Macrophage pigment	0/10	0/10	0/10	0/10	0/10	10/10** (1.0)
Females						
Hepatocyte necrosis	0/10	0/10	0/10	0/10	8/10** (1.3)	10/10** (2.8)
Macrophage pigment	0/10	0/10	0/10	0/10	0/10	10/10** (2.0)

[a](Severity score) based on a scale of 1 to 4; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked. Severity scores are averages based on the number of animals with lesions from groups of 10.
**Significantly different from control, p <0.01.

In the mice, no substance-induced mortality was observed. 5 Male mice died of undetermined causes during the study, 3 in the lowest exposure group and one, each at 100 and 200 ppm, thus suggesting that DMF exposure was not involved. All female mice survived until termination of the study. Body weight gains were slightly reduced (approximately 29 % less than controls) in female mice exposed to 800 ppm (Table B26). Relative liver weights were increased in both sexes at all exposure concentrations without a clear dose-response relationship (Table B27). Minimal to mild cenrilobular hypertrophy was observed in all groups of male mice and in female mice exposed at 100 ppm and higher concentrations (Table B28). In females there was a significant trend toward an increase in the estrous cycle lenght, however significantly prolonged estrus and diestrus was observed only in females exposed to 200 ppm. In summary, hepatocellular hypertrophy or increased liver weights occurred at all exposure concentrations and body weight gain was reduced in the females at the highest concentration tested. The NOAEC was 50 ppm for female mice, but a NOAEC based upon the absence of microscopic liver injury was not determined in male mice. However, in OECD SIDS report is mentioned that since in chronic inhalation studies in rats and mice (see above (Malley et al., 1994)) no increased incidence of hepatic tumors occurred, the hepatocellular hypertrophy can be regarded as the result of an adaptive process, thus the NOAEC for mice is expected to be at about 400 ppm.

Table B26. Survival and Weight Gain of B3C6F1 Mice in the 13-Week Inhalation Studies of N,N-Dimethylformamide.

Exposure concentration (ppm)	Survival[a]	Mean body weights			Final Weights relative to Controls (%) [d]
		Initial	Final[b]	Change[c]	
MALES					
0	10/10	26.2	34.0	7.8	
50	7/10	25.4	33.5	8.1	99
100	9/10	26.2	30.6	4.4	90
200	9/10	26.2	34.3	8.1	101
400	10/10	26.7	33.2	6.5	98
800	10/10	24.6	30.9	6.3	91
FEMALE					
0	10/10	21.1	25.2	4.1	
50	10/10	21.4	26.3	4.9	104
100	10/10	22.0	27.2	5.2	108
200	10/10	21.2	28.6	7.4	114

Exposure	Survival[a]	Mean body weights			Final Weights
400	10/10	20.8	27.0	6.2	107
800	10/10	21.7	24.6	2.9	98

[a] Number surviving at 13 weeks/number of animals per dose group.
[b] At necropsy.
[c] Mean weight change of the animals in each dose group.
[d] (Dosed group mean/Control group mean) x 100.

Table B27. Absolute and Relative Liver Weights in Mice Exposed to Inhaled DMF for 13 Weeks. (Table 5. From Lynch et al., 2003).

	DMF concentration (ppm)					
	0	**50**	**100**	**200**	**400**	**800**
Males						
Absolute	1.67 ± 0.04[a]	1.91 ± 0.04	1.57 ± 0.07	2.07 ± 0.05**	2.02 ± 0.08**	1.94 ± 0.12**
Relative	4.91 ± 0.01[b]	5.69 ± 0.13*	5.13 ± 0.15*	6.05 ± 0.05**	6.07 ± 0.12**	6.24 ± 0.21**
Females						
Absolute	1.17 ± 0.05	1.31 ± 0.04*	1.48 ± 0.04**	1.76 ± 0.05**	1.70 ± 0.03**	1.51 ± 0.04**
Relative	4.64 ± 0.12	4.97 ± 0.08*	5.42 ± 0.09**	6.14 ± 0.12**	6.29 ± 0.10**	6.16 ± 0.13**

[a]Mean ± SE (g); 10 animals/group except 50 ppm males (n=7) and 100 and 200 ppm males (n=9).
[b]Organ weight/body weight X 100; mean of individual ratios.
*Significantly different from control, p<0.05.
**Significantly different from control, p<0.01.

Table B28. Incidence of Liver Lesions Observed in Mice Exposed to Inhaled DMF for 13 weeks. (Table 6 from Lynch et al., 2003).

	DMF concentration (ppm)					
	0	**50**	**100**	**200**	**400**	**800**
Centrilobular hepatocellular hypertrophy						
Males	0/10	4/10* (1.8)a	9/10** (1.3)	10/10** (2.0)	10/10** (2.0)	10/10** (2.0)
Females	0/10	0/10	10/10** (1.3)	10/10** (1.9)	10/10** (2.0)	10/10** (2.0)

[a](Severity score) based on a scale of 1 to 4; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked. Severity scores are averages based on the number of animals with lesions from groups of 10.
*Significantly different from control, p< 0.05.
**Significantly different from control, p< 0.01.

Senoh et al., 2003

F344 rats and BDF1 mice of both sexes were exposed to DMF by inhalation (6 h/d × 5 d/wk) to 100, 200, 400, 800 or 1,600 ppm DMF for 2 weeks, and 50, 100, 200, 400 or 800 ppm DMF for 13 weeks. Three male and 7 female rats died during the 2-week exposure to 1,600 ppm DMF, but no death of the exposed rats or mice occurred under any other exposure conditions. Massive, focal and single cell necroses were observed in the liver of DMF-exposed rats and mice (Table B29). The massive necrosis associated with the centrilobular fibrosis occurred at the highest exposure concentration. The single cell necrosis was associated with fragmentation of the nucleoli as well as an increased mitotic figure. The 13-week exposures of rats and mice to DMF were characterized by increases in the relative liver weight and the incidence of the centrilobular hepatocellular hypertrophy as well as increased serum levels of AST, ALT, LDH, total cholesterol and phospholipid. Lower confidence limits of the benchmark dose yielding the response with a 10 % extra risk ($BMDL_{10}$) were determined for the relative liver weight and the incidence of hepatocellular hypertrophy of the 13-week exposed animals (Table B30). For the increased relative liver weight, the $BMDL_{10}$ value resulted in 1.1 and 13.1 ppm for male and female rats, and 1.1 ppm for male mice, respectively. Nevertheless, the $BMDL_{10}$ value for the relative liver weight of female mice was not determined because of insignificant changes in the relative liver weight

throughout the range of exposure concentrations. For the hepatocellular hypertrophy, the $BMDL_{10}$ value resulted in 68.5 and 191 ppm for male and female rats, and 17.5 and 372.5 ppm for male and female mice, respectively. These $BMDL_{10}$ values for hepatocellular hypertrophy are consistent with the finding by Lynch et al. 2003 that the NOAEL of hepatocellular hypertrophy were 50 and 200 ppm for female mice and rats of both sexes, respectively.

Table B29. Incidences of liver lesions in the rats and mice exposed to DMF vapour by inhalation for 13 weeks.

(A) Rats	Male						Female					
Group (ppm)	**Con-trol**	**50**	**100**	**200**	**400**	**800**	**Con-trol**	**50**	**100**	**200**	**400**	**800**
Number of animals examined	10	10	10	10	10	10	10	10	10	10	10	10
Necrosis: single cell	0	0	0	8**	10**	10**	0	0	0	8**	9**	10**
Necrosis: massive	0	0	0	0	0	0	0	0	0	0	0	1
Necrosis: focal	0	0	0	0	0	0	0	0	0	0	0	0
Necrosis: centrilobular	0	0	0	0	0	0	0	0	0	0	0	0
Centrilo-bular hypertrophy	0	0	0	3	8**	9**	0	0	0	0	8**	10**
(B) Mice	**Male**						**Female**					
Group (ppm)	**Con-trol**	**50**	**100**	**200**	**400**	**800**	**Con-trol**	**50**	**100**	**200**	**400**	**800**
Number of animals examined	10	10	10	10	10	10	10	10	10	10	9[a]	10
Necrosis: single cell	0	0	0	0	1	6*	0	0	0	0	0	5*
Necrosis: massive	0	0	0	0	0	3	0	0	0	0	0	0
Necrosis: focal	0	0	4	2	3	4	0	1	6*	5*	7*	1
Necrosis: centrilobular	0	0	0	0	0	1	0	0	0	0	0	0
Centrilo-bular hypertrophy	0	4*	10**	10**	10**	10**	0	0	0	0	0	7*

Significant difference; *:p≤0.05 **:p≤0.01 by Chi-square test.,
[a] Number of female mice examined was 9 instead of 10, because one mouse accidentally died

Table B30. $BMDL_{10}$ and NOEL values for the relative liver weights and the incidences of the single cell necrosis and the centrilobular hypertrophy of rats and mice exposed to DMF vapour by inhalation for 13 weeks.

(A) Rats	Sex	Incidences of lesions						NOEL (ppm)	$BMDL_{10}$ and Model fitting			
Group		**Co**	**50**	**10**	**20**	**40**	**800**		**$BMDL_{10}$**	**Model**	**p-**	**AIC**

(ppm)		ntrol		0	0	0			(ppm)		value	
Number of animals examined		10	10	10	10	10	10					
Single cell necrosis	M	0	0	0	8**	10**	10**	100	91.5	Gamma	0.9983	12.493
	F	0	0	0	8**	9**	10**	100	59.8	Quantal quadratic	0.3011	26.836
Centrilobular hypertrophy	M	0	0	0	3	8**	9**	200	68.5	Gamma	0.5515	36.028
	F	0	0	0	0	8**	10**	200	191.0	Weibull	10.000	14.008
Relative liver weight (%)	M	2.59	2.90	2.96*	3.03**	3.05*	3.20**	50	1.1	Linear (log)	0.2448	224.98
	F	2.40	2.56	2.62	2.70**	2.89**	3.68**	100	13.1	Polynomial	0.2201	152.21

(B) Mice	Sex	Incidences of lesions						NOEL (ppm)	$BMDL_{10}$ and Model fitting			
Group (ppm)		**Control**	**50**	**100**	**200**	**400**	**800**		**$BMDL_{10}$ (ppm)**	**Model**	**pvalue**	**AIC**
Number of animals examined		10	10	10	10	10a	10					
Single cell necrosis	M	0	0	0	0	1	6*	400	251.8	Gamma	0.9996	24.057
	F	0	0	0	0	0	5*	400	377.4	Weibull	10.000	15.863
Centrilo- bular hypertrophy	M	0	4*	10**	10**	10**	10**	-	17. Mai	Gamma	10.000	15.489
	F	0	0	0	0	0	7*	400	372.5	Weibull	10.000	14.217
Relative liver weight (%)	M	Apr 13	4.77**	5.08**	5.15**	5.19**	5.26**	-	1.1	Linear (log)	0.3062	135.59
	F	4.53	4.79	4.89	5.01	5.00	5.17	-	-	-	-	-

*: $p<0.05$ and **: $p<0.01$ for the liver weight by Dunnett's test, and for the histopathological parameters by Chi-square test

Senoh et al., 2004

In a follow-up chronic study, rats and mice were exposed by inhalation to DMF vapour at a concentration of 0, 200, 400 or 800 ppm (v/v) for 6 h/d, 5 d/wk, for 104 weeks. The highest dose selected exceeded the maximum tolerated dose (MTD), which was exacerbated by probable exposure to an aerosol during atmosphere generation. Liver weights increased in both rats and mice exposed to DMF at 200 ppm and above (Table B31). Increased levels of γ-GTP, ALT, AST and total bilirubin in exposed rats of both sexes and AST and ALT in exposed mice of both sexes were noted. Besides this, DMF increased incidences of hepatocellular adenomas and carcinomas in rats and incidences of hepatocellular adenomas, carcinomas and hepatoblastomas in mice, and that hepatocarcinogenicity of DMF was more potent in mice than in rats (see Carcinogenicity section).

Table B31. Number of surviving animals, body weight and absolute and relative liver weight (mean ± SD) of the rats and mice exposed to DMF vapours by inhalation for 2 years.

Rats	Male					Female				
	No. of surviv.	**Body weight**		**liver weight**		**No. of surviv.**	**Body weight**		**liver weight**	
		(g)	**(%)**	**absolute (g)**	**relative (%)**		**(g)**	**(%)**	**absolute (g)**	**relative (%)**

Control	42/50	393 ± 41	–	11.176 ± 1.718	3.1 ± 0.5	42/49	277 ± 32	–	7.033 ± 1.044	2.7 ± 0.5
200 ppm	38/50	366 ± 29*	93	13.292 ± 2.103**	4.0 ± 0.7**	38/50	254 ± 25	92	7.880 ± 1.554*	3.3 ± 0.5**
400 ppm	40/50	340 ± 25**	87	12.237 ± 2.390	3.8 ± 0.8**	38/50	213 ±21**	77	7.462 ± 1.312	3.7 ± 0.9**
800 ppm	37/50	299 ± 18**	76	15.774 ± 3.072**	5.7 ± 1.2**	30/50	196 ±13**	71	9.176 ± 1.448**	5.0 ± 0.8**

Mice	**Male**					**Female**				
	No. of surviv.	**Body weight**		**liver weight**		**No. of surviv.**	**Body weight**		**liver weight**	
		(g)	**(%)**	**absolute (g)**	**relative (%)**		**(g)**	**(%)**	**absolute (g)**	**relative (%)**
Control	37/50	49.2 ± 7.6	–	1.724 ± 0.411	3.9 ± 1.2	29/49	33.7 ± 4.0	–	1.570 ± 0.325	5.4 ± 1.4
200 ppm	33/50	42.6 ± 3.8	87	4.162 ± 2.421**	11.0 ± 6.1**	30/50	33.6 ± 3.7	100	5.535 ± 2.582**	18.9 ± 7.0**
400 ppm	37/49	38.2 ± 3.3**	78	4.570 ± 2.441**	13.7 ± 6.3**	21/50	32.0 ± 2.7	95	7.100 ± 1.299**	25.8 ± 3.7**
800 ppm	40/50	34.5 ± 2.7**	70	5.406 ± 0.878**	17.8 ± 2.5**	22/49	27.3 ± 2.1**	81	5.671 ± 0.967**	23.6 ± 3.0**

Significant difference:
*: p≤0.05 **: p≤0.01 by Dunnett's test. Body weight measured on the last exposure day (%: compared to the respective control). Relative liver weight: liver weight/body weight measured at time of necropsy.

Ohbayashi et al., 2008

Male Wistar rats were exposed by inhalation to N,N-dimethylformamide (DMF) at 0 (control), 200 or 400 ppm (v/v) for 6 hr/day, 5 days/week and 4 weeks, and each inhalation group received DMF-formulated drinking water at 0, 800, 1,600 or 3,200 ppm (w/w) for 24 hr/day, 7 days/week and 4 weeks. Both the combined inhalation and oral exposures and the single-route exposure through inhalation or ingestion induced centrilobular hypertrophy and single-cell necrosis of hepatocytes, increased plasma levels of alanine aminotransferase (ALT), increased percentage of proliferating cell nuclear antigen (PCNA)-positive hepatocytes without glutathione-S-transferase placental form (GST-P)-positive liver foci, and increased relative liver weight (Table B32). Those hepatic parameters of the DMF-induced effects were classified into hypertrophy, necrotic and proliferative responses according to the pathological characteristics of affected liver. While magnitudes of the hypertrophic and necrotic responses were linearly increased with an increase in amounts of DMF uptake in the single-route exposure groups, those dose-response relationships tended to level off in the combined-exposure groups. Saturation of the hypertrophic and necrotic responses at high dose levels might be attributed to suppression of the metabolic conversion of DMF to its toxic metabolites. Percentage of PCNA-stained hepatocytes classified as the proliferative response was increased more steeply in the combined-exposure groups than in the single-route exposure groups. It was suggested that the proliferative response of hepatocytes to the combined exposures would be greater than that which would be expected under an assumption of additivity for the component proliferative responses to the single-route exposures through inhalation and ingestion.

Table B32. Changes in hepatic parameters following combined inhalation and oral exposures or single-route exposures to DMF in male rats.

Group name	**No. of animals examined**	**Liver weight (%, mean ± S.D.)**	**Centrilobular hypertrophy**		**Single-cell necrosis**		**ALT (IU/L) (mean ± S.D.)**	**PCNA positive hepatocytes (%, mean ± S.D.)**
			Incidence (%)	**(Averaged severity)**	**Incidence (%)**	**(Averaged severity)**		
Inh-0 + Orl-0	5	3.10 ± 0.05	0	0	0	0	35 ± 1	0.3 ± 0.1

Group name	No. of animals	Liver weight (%,	Centrilobular hypertrophy		Single-cell necrosis		ALT (IU/L)	PCNA positive hepatocytes (%,
ppm								
Inh-0 + Orl-800 ppm	5	4.08 ± 0.17a	100	(1.0)	60	(0.6)	51 ± 10	1.0 ± 0.5
Inh-0 + Orl-160 0 ppm	5	4.11 ± 0.09[a]	80	(0.8)	80	(1.0)	53 ± 7	1.6 ± 0.6[a]
Inh-0 + Orl-320 0 ppm	5	4.23 ± 0.21[a]	100	(1.0)	100	(1.8)	76 ± 15[a]	2.6 ± 1.8[a]
Inh-200 + Orl-0 ppm	5	3.74 ± 0.13	40	(0.4)	100	(1.4)	60 ± 12a	0.6 ± 0.2[a]
Inh-200 + Orl-800 ppm	5	3.93 ± 0.16	100	(1.2)	100	(2.0)	88 ± 14[a]	1.9 ± 0.6[a,b]
Inh-200 + Orl-160 0 ppm	5	4.01 ± 0.36[a]	100	(1.6)	100	(2.0)	93 ± 26[a,b]	3.6 ± 2.4[a,b]
Inh-200 + Orl-320 0 ppm	5	3.97 ± 0.11[a]	100	(1.8)	100	(2.4)	97 ± 20[a,b]	5.8 ± 1.5[a,b,c]
Inh-400 + Orl-0 ppm	5	4.03 ± 0.12a	100	(2.0)	100	(2.0)	122 ± 27[a]	1.4 ± 0.7[a]
Inh-400 + Orl-800 ppm	5	4.10 ± 0.04[a]	100	(1.8)	100	(2.8)	85 ± 17[a,c]	2.6 ± 1.0[a,c]
Inh-400 + Orl-160 0 ppm	5	3.98 ± 0.19[a]	100	(2.0)	100	(2.0)	95 ± 21[a,c]	3.6 ± 2.0[a]
Inh-400 + Orl-320 0 ppm	5	4.07 ± 0.17[a]	100	(2.0)	100	(2.4)	134 ± 53 [a,c]	4.4 ± 1.9 [a,b]
DMF single-route exposure groups								
Regression equation			y = 0.0046x + 0.1942		y = 0.0066x + 0.1613		y = 0.221x + 33.719	y = 0.0068x + 0.2564
DMF combined-exposure groups								
Regression equation			y=0.0037x + 0.3574		y = 0.0041x + 0.6926		y = 0.1542x + 42.322	y = 0.0086x + 0.5523

a, b, c: Significantly different from untreated control group (Inh-0 + Orl-0 ppm), each inhalation-alone group (Inh-200 + Orl-0, Inh-400 + Orl-0) with matching concentrations and each oral-alone group (Inh-0 + Orl-800, Inh-0 + Orl-1600, Inh-0 + Orl-3200) with matching concentrations, respectively, at p

< 0.05 by Dunnett test.
PCNA : Proliferating cell nuclear antigen

TSCATS, 1990

The study was performed to characterize the toxic effects of DMF in Cynomolgus monkeys following 13 weeks of inhalation exposure. The aim was to determine the target organ effects, concentration response, a NOAEL, to measure selected pharmacokinetic parameters, evaluate potential toxic effects on the male and female reproductive system, examine differences in response between sexes and to evaluate potential specimen differences in toxic responses (comparison with literature data) following exposure to DMF vapours. A total of 20 male and 12 adult female monkeys were required for this study. Three monkeys/sex/exposure group were exposed to the three concentrations of DMF (30, 100 or 500 ppm) or filtered room air (concurrent control). In addition, two males per exposure group were designated as the post-exposure group. The post-exposure group was held for 13 additional weeks with no exposure and was then necropsied.

The effects of the test substance were studied in groups of 5 male and 3 female monkeys (two males/group served as additional animals for the post-exposure period). There were no early deaths in this study and all animals were sacrificed on their scheduled day of necropsy. There were no treatment-related findings in the 13 week inhalation study except possible alterations in the menstrual cycle of DMF exposed females. The menstrual cycle of 1 low dose group female, 2 mid dose females and all high dose females were altered in length. According to the authors, the subchronic exposure of cynomolgus monkeys to DMF did not cause any adverse health effects (liver function, sperm production, and sperm motility appeared unaffected). With respect to the possible increase in mensis length with exposure to DMF and its relevance, the experts conclusions were that while the data are suggestive of an effect, there is no confirmed evidence that DMF caused an effect on menstrual cycle because of the monkeys recent importation history and lack of preexposure data. NOAEl of 500 ppm was established for monkeys.

Summary of findings in old repeated dose studies in different species.

Cats and rabbits exposed to DMF by inhalation (75, 125 and 150 mg/L on the first, second and third day, respectively) showed overt findings (salivation, accelerated breathing, strong excitation, redness of the ears). The animals died during exposure or some hours later. With the exception of fatty infiltration in the liver of the cat and broncho-pneumonic foci in the lungs of the rabbit, no other pathological findings were observed at necropsy BASF AG, 1952, cited in OECD SIDS, 2004).

In another study, rats and mice were exposed to 150, 300, 600, 1200 ppm (ca. 0.45, 0.91, 1.82, 3.63 mg/L) DMF 5 d/w; 6 h/d during 12 weeks (TSCATS, 1984). The highest concentration led to deaths, significant reduced body weight gain and clinical signs in both species. In rats, a dose-related increase of serum cholesterol was observed, significant at the highest concentration tested and at 600 ppm in the females. Due to a significant increase of serum alkaline phosphatase in female animals of the 600 and 1200 ppm groups and elevated enzyme values (SGPT, SGOT) in one animal at the highest concentration tested as well as to macroscopical and histopathological changes in the liver (fibrosis, dark stained cytoplasm of hepatocytes and in the two animals of the 1200 ppm group that died before scheduled sacrifice widespread collaps, necrosis and accumulation of yellow-brown pigment in kupffer cells, macrophages and hepatocytes was seen), the liver seemed to be the target organ. Microscopic changes in the liver were predominantly found in the high dose group and to a lesser extent at 600 ppm and in the form of variation in nuclear size and cytoplasmic characteristics at 300 ppm. In mice, discolored livers and/or alterations in consistency were the main findings at gross necropsy at both high concentrations (600 and 1200 ppm). Microscopically, animals of these dose groups showed areas of collapse (according to the authors residual of necrosis) or liver necrosis and one mouse of the 300 ppm group showed a large area of coagulative necrosis. Two mice of the highest concentration group that died 71 and 76 days after exposure started, exhibited hepatic single cell necrosis. Hepatic cytomegaly around central veins was seen in all exposed groups and the incidence and severity were dose-related. According to the authors the MTD was below 600 ppm.

In a study with rats exposed to aerosol of DMF (concentrations are not reported) during 30 days, except necroses in liver and kidneys and changes in lungs, changes in arterial vessel of the myocard were mentioned (Santa Cruz et al., 1978, cited in OECD SIDS, 2004).
In other numerous old inhalation studies with cats, dogs, guinea pigs, rabbits and rodents the major effect of DMF inhalation was on the heart, liver, pancreas, kidneys, adrenals and thymus (OECD SIDS; 2004). Among the species, dogs were reported to be more susceptible specie to the impact of DMF on heart than on liver parameters.

Dermal

There are results of old dermal studies of different durations reported for rats, rabbits, and guinea pigs (OECD SIDS, 2004). In rats exposed dermally to 215, 430, 960, 4800 mg/kg during 30 days, dose-related changes in GOT, GPT, Alkaline Phosphatase, Cholinesterase, GGT and in the lipid fraction in the serum and in the liver homogenate were described. The NOAEL was 215 mg/kg (Bainova and Antov, 1980, cited in OECD SIDS, 2004). In another rat study, functional, biochemical and pathomorphological changes were described for the liver and the lipid metabolism (Bainova et al., 1981, cited in OECD SIDS, 2004). A cumulative effects of DMF was suggested after dermal repeated exposures in rats, treated by 475 mg/kg bw during 30 days and then, treated once with 11.140 mg/kg bw (corresponding to the dermal LD_{50}) (Schottek, 1970, cited in OECD SIDS, 2004). Thereafter all animals died within 48 hours. Due to this finding the authors deduce a cumulative effect of DMF exposures by the dermal route.
In a study with rabbits, exposed to 1000 mg/kg bw 2h/ day during 25 days, local hyperemia and slight infiltration as well as scaling were seen (Lobanowa, 1958, cited in OECD SIDS, 2004. In another study, dermal administration of the test substance at 2000 mg/kg bw to a group of 6 rabbits during two weeks (9 applications) resulted in reduced body weights in the dosed group (TSCATS: OTS 0520867, 1960). Three animals were found dead 2 days after the 5th application, one died 2 days after the 9th application. The remaining 2 rabbits were sacrificed 4 and 11 days after the 9th application. Only 2 of the animals that died had sufficiently well preserved tissues for a histological appraisal; these animals exhibited histological evidence of liver injury. In the rabbit sacrificed 4 days after the last dosing, focal acute inflammatory lesions of the lungs and kidneys and chronic inflammatory lesions of the liver were found, however, according to the authors, this was not substance-related. The animal sacrificed 11 days after the last dosing exhibited only chronic nephritis.
Guinea pigs exposed to ca. 13000 mg/kg, up to 8 days died after 7-8 applications (Martelli, 1960, cited in OECD SIDS, 2004). Significantly decreased food consumption was recorded; convulsions were observed. Necropsy revealed hyperemia of the internal organs and damage of the liver and the spleen.

Overall repeated dose studies

An overview of the key studies identified in the sections above is presented in Table B37 per route of administration, followed by a section on conclusions on repeated dose toxicity. In Table B34 the PODs for risk assessment are presented for systemic effects (local effects are covered by systemic effects).

Table B33. Key studies with repeated administration of DMF (adopted from registration dossier and OECD SIDS, 2004).

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia-bility*	Reference
Oral				
rat (Sprague-Dawley) male/female, 10/ sex/dose group equivalent or similar to OECD Guideline	subacute (oral: gavage) 250, 500, 1000 and 2000 µL/kg (~238, 475, 950, 1900 mg/kg) (nominal in water) Vehicle: water	NOAEL: 238 mg/kg bw/day (nominal) (male/female) (overall effects) LOAEL: 475 mg/kg bw/day (nominal)	2	BASF AG (1977) OECD SIDS (2004)

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia-bility*	Reference
407 (Repeated Dose 28-Day Oral Toxicity in Rodents)	Exposure: 28 days (5 d/w)	(male/female) (body weight)		
rat (Charles River CD strain) male/female Weanling rats were exposed	subchronic (oral: feed) 200, 1000, 5000 ppm in the diet (ca. 12, 60, 300 mg/kg) Exposure: 90 days (continuously in diet)	NOAEL: 200 ppm (male/female) LOAEL: 1000 ppm (male/female)	2	TSCATS: OTS 0520880 (1960) TSCATS: OTS 0571664 (1960) TSCATS: OTS 0572893 (1960)
rat (Wistar) male Male Wistar rats	subacute (oral: drinking water) 100, 500, 1000 ppm in the drinking water (ca. 9.1, 45.5, 90.9 mg/kg/d) Vehicle: tap water Exposure: 14 or 49 days (continuously in drinking water)	7-Ethoxycoumarin 0-deethylase activity, microsomal UDP-glucuronosyltransferase, liver GSH (reduced glutathione) increased,: All the attempts to demonstrate formaldehyde liberation as the product of oxidative N-demethylation of DMF in liver microsomes failed. No DMF-dependent N-demethylation activity. GSH concentration in the kidneys slightly increased. markedly diminished enzyme activity of cytosolic formaldehyde dehydrogenase both in liver and kidney tissues. decreased hepatic activity of propionaldehyde-dehydrogenase. DMF itself or its known metabolite, monomethylformamide, had no effect on the activities of various soluble aldehyde dehydrogenases of the liver *in vitro.* Kinetic enzyme measurements of various aldehyde dehydrogenases or of alcohol dehydrogenase following	2	E. Elovaara, M. Marselos' and H. Vainio (1983) OECD SIDS (2004)

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia-bility*	Reference
		the exposure of freshly isolated hepatocytes for 2 hours to DMF (510 mM) via the incubation medium did not substantiate any occurrence of enzyme inhibition.		
Inhalation				
rat (Crl:CD BR) male/female, 87 /sex /dose combined repeated dose and carcinogenicity (inhalation) (whole body) OECD Guideline 451	25, 100, 400 ppm (~0.08, 0.3, 1.21 mg/L) Vehicle: clean air Exposure: 2 years (5 d/w, 6 h/d)	NOEC: 25 ppm (male/female) (body weight changes, clinical chemistry changes) LOEC: 100 ppm (male/female) (hepatotoxic effects)	2	Malley, L.A., Slone, T.W. Jr., Van Pelt, C., Elliott, G.S., Ross, (1994a)
mouse (Crl:CD-1 (ICR)BR) male/female, 78 /sex /dose combined repeated dose and carcinogenicity (inhalation) (whole body) OECD Guideline 451	25, 100, 400 ppm (~0.08, 0.30, 1.21 mg/L) Vehicle: clean air Exposure: 18 months (5 d/w, 6 h/d)	NOEC: 400 ppm (male/female) based on: act. ingr. (oncogenicity (no effects)) LOAEC: ca. 25 ppm (male/female) ((general toxicity) only minimal changes in liver at this concentration)	2	Malley, L.A., Slone, T.W. Jr., Van Pelt, C., Elliott, G.S., Ross, (1994a)
rat (Fischer 344) male/female subchronic (inhalation), 10 /sex /group equivalent or similar to OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day)	50, 100, 200, 400, 800 ppm (ca. 0.15, 0.30, 0.61, 1.21, 2.43 mg/L) Vehicle: unchanged (no vehicle) Exposure: 13 weeks (5 days/week, 6 hours/day)	NOAEC: 100 ppm (male/female) LOAEC: 200 ppm (male/female) (microscopic liver lesions)	2	NTP report (1992); Lynch, D. W., Placke, M. E., Persing, R. L., and Ryan, M. J. (2003)
mouse (B6C3F1) male/female, 10/sex /group equivalent or similar to OECD Guideline 413	50, 100, 200, 400, 800 ppm (ca. 0.15, 0.30, 0.61, 1.21, 2.43 mg/L) Vehicle: unchanged (no vehicle) Exposure: 13 weeks (5 days/week, 6 hours/day)	No NOAEC identified. (For female mice the NOAEC for microscopic liver lesions is close to 50 ppm, however increased liver weights were observed at this	2	NTP report (1992); Lynch, D. W., Placke, M. E., Persing, R.

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia-bility*	Reference
(Subchronic Inhalation Toxicity: 90-Day)		concentration. A NOAEC could not be defined in male mice, as centrilobular hepatocellular hypertrophy and increased liver weights were observed at all DMF exposure concentrations.		L., and Ryan, M. J. (2003)
rat and mice (F344/DuCrj rats & Crj:BDF1 mice) male/female, 10/sex /group OECD Guideline 412 (Repeated Dose Inhalation Toxicity: 28/14-Day) OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day)	100, 200, 400, 800 and 1600 ppm during the 2-wk exposure (nominal conc.) 50, 100, 200, 400 and 800 ppm during the 13-wk exposure (nominal conc.) Vehicle: unchanged (no vehicle) Exposure: 6h/d (5d/wk 2wk and 13 wk)	NOAEC: 400 ppm (male/female) (mice) NOAEC: 100 ppm (male/female) (rats) $BMDL_{10}$: 1 ppm (male/female) (increased liver weight) $BMDL_{10}$: 17 ppm (male) (for hepatocellular hypertrophy)	3 (see Conclusion for Carcinogenicity)	Senoh, H. , Katagiri, T., Arito, H., Nishizawa, T., Nagano, K., Yamamoto (2003)
rat and mice (F344/DuCrj rats & Crj:BDF1 mice) male/female, 50/sex /group OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies)	0, 200, 400 and 800 ppm Vehicle: unchanged (no vehicle) Exposure: 6h/d (5d/wk , 104 weeks)	No NOAEC identified: Liver weights increased in both rats and mice exposed to DMF at 200 ppm and above (regarding neoplastic findings, please see section "Carcinogenicity")	3 (see Conclusion for Carcinogenicity)	Senoh, H., Aiso, S., Arito, H., Nishizawa, T., Nagano, K., Yamamoto, S., and Matsushima, T. (2004)
rat (F344/DuCrlCrj rats (SPF), males, 5/group OECD guidelines 407 and 412; 5 rates/ group were used instead of 10.	0, 200 and 400 ppm (additionally, each inhalation group received DMF-formulated drinking water at 0, 800, 1,600 or 3,200 ppm (w/w) for 24 hr/day, 7 days/week and 4 weeks. Vehicle: DMF vapour-air mix Exposure: 6h/d (5d/wk , 4 weeks)	No NOAEC identified (inhalation and oral exposures enhanced the hepatocellular proliferation in a more than additive manner (synergistically) Findings: centrilobular hypertrophy and single-cell necrosis of hepatocytes, increased plasma levels ALT, increased percentage of PCNA-positive hepatocytes without glutathione-S-transferase placental form (GST-P)-positive liver foci, and increased relative liver	3 (see Conclusion for Carcinogenicity)	Ohbayashi, H., Yamazaki, K., Aiso, S., Nagano, K., Fukushima, S., and Ohta, H. (2008)

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia-bility*	Reference
		weight		
monkey (Cynomolgus) male/female subchronic (inhalation)	30, 100, 500 ppm (about 0.09, 0.3, 1.5 mg/L) Exposure: 13 weeks (5 d/w, 6 h/d)	NOAEC: 500 ppm (male/female)	2	TSCATS: OTS 0528444 (1990)

* reliability is based on the Klimisch code (Klimisch et al., 1997).

Conclusion

The systemic effects of DMF observed in the oral repeated dose toxicity studies were reduced body weight and reduced food consumption. Hepatic injury was characterized by changes in clinical chemistry values, e.g. increased enzyme activities, increased liver weights and hemorrhagic liver dystrophy with necrosis. Besides this increased kidney weights were reported in the 28-day gavage study. The liver was the predominant organ of DMF toxicity. Additionally, DMF impaired aldehyde oxidation in liver and kidneys of the rat after the DMF intake in the sub-acute study. This could explain the mechanism behind the alcohol intolerance observed in man after DMF exposure. The NOAEL of 238 mg/kg bw and 200 ppm in diet (12 mg/kg bw) were established for rats in the oral 28-day and oral 90-day studies, respectively. The 28-day study was preferred to derive POD over the 90-day study as the most reliable study available. Indeed the 90-day study is indicated in the registration dossier as supporting study performed on weanling rats. The POD for systemic dermal effects was derived by route-to-route extrapolation (see section DNEL derivation). No POD is established for local effects since DMF is not irritating to skin.

Repeated dermal exposures of DMF to rats, rabbits and guinea pigs resulted in deaths, clinical signs, dose-related changes in the liver' enzyme activities and in damage of variety of organs. Among pathomorphological changes were inflammatory lesions of the lungs, kidneys, liver and spleen. The results of these studies cannot be taken into account for the risk assessment since only abstracts are available as reported in the ECHA dissemination website.

The inhalation studies showed a consistent NOAEC in rodent species. Chronic NOAEC of 25 ppm (80 mg/m³) and LOAEC of 25 ppm and subchronic NOAEC of 100 ppm (300 mg/kg bw) and 400 ppm (1210 mg/m³) were established for rats and mouse, respectively. The subchronic NOAEC was confirmed by two studies (NTP, 1992, Senoh et al., 2003). The target organ was liver. The toxicity manifested by the increased serum levels of liver' enzymes, total cholesterol, bilirubin and phospholipid as well as increased liver weights with centrilobular hepatocellular hypertrophy and hepatic single cell necrosis. The 2-year study was used to derive the POD. NOAEC of 80 mg/m³ (25 ppm) served as POD for systemic effects by long-term exposures. No POD is established for local effects since DMF is not irritating to respiratory tract. There were no compound-related lesions noted in the nose or respiratory tract for any exposure concentration in both rats and mice during the long-term inhalation study (Malley et al., 1994).

Table B34. Point of departures for DNEL derivation for repeated dose toxicity.

POD for DNEL derivation (endpoint)	Species and duration	NOAEL (mg/kg bw) or NOAEC ppm (mg/m³)	Toxicological endpoint	Reference
Systemic				
Inhalation	Rats, 2-years	25 ppm (80 mg/m³)	Decreased body weights,	Malley et

POD for DNEL derivation (endpoint)	Species and duration	NOAEL (mg/kg bw) or NOAEC ppm (mg/m³)	Toxicological endpoint	Reference
			clinical chemistry changes, liver injury	al., 1994
Dermal	Rats, 28-days	238 mg/kg bw	Reduced body weights and food consumption, clinical chemistry changes, liver injury	BASF, 1977

B.5.7. Mutagenicity

DMF is not mutagenic in any of the *in vitro* or *in vivo* mutagenicity tests (the registration dossier and OECD SIDS, 2004).

B.5.8. Carcinogenicity

Information was obtained from the registration dossier, OECD SIDS (2004), and publications.

Inhalation

In a chronic toxicity/oncogenicity study, male and female rats (Crl: CD BR) and mice (Crl: CD-1 (ICR) BR) were exposed by inhalation to DMF for 6 hours per day, 5 days per week for 18 months (mice) or 2 years (rats) at concentrations of 0, 25, 100, or 400 ppm (OECD 451, Malley, et al. 1994). In the rats body weight and body weight gain were reduced in both sexes at 400 ppm and in the male animals at 100 ppm. Moreover, the animals in these groups showed increased enzyme activity, increased liver weights and some histopathological findings in the liver (see section Repeated dose toxicity). There was no compound related increase of tumors (Table B35, Table B36). Similar findings were observed in mice. There were no compound-related effects detected on the estrous cycles of rats and mice exposed to concentrations up to 400 ppm. The hepatic enzyme sorbitol dehydrogenase (SDH) activity was increased in rats exposed at 100 and 400 ppm. The magnitude of elevation for SDH activity was small and the lack of consistent elevations of alanine aminotransferase and aspartate aminotransferase activities in both males and females indicate that the hepatocellular injury was mild. For both species, microscopic compound-related changes were only observed in the liver. In rats, exposure at 100 or 400 ppm caused an increase in the ratio of liver weight to body weight, hepatocellular hypertrophy, pigment accumulation, and single cell necrosis. In mice, exposure to DMF at 100 or 400 ppm caused an increase in the ratio of liver weight to body weight, hepatocellular hypertrophy, and pigment accumulation. Increased hepatic single cell necrosis was observed at 25, 100, and 400 ppm. Varying types of non-neoplastic hepatic foci of alteration were increased in mice at 100 ppm and above. No effects were seen in the reproductive tissues and organs during this study. The respiratory tract was unaffected. In rats and mice, DMF did not produce an oncogenic response. Therefore, the no-observable-effect level (NOEL) for oncogenicity was 400 ppm in both rats and mice. The NOEL in rats is 25 ppm based on the body weight changes, clinical chemistry changes, and hepato-toxic effects observed at 100 and 400 ppm. Although a NOEL was not attained in mice due to the morphological changes observed in the liver at all three test concentrations, the NOEL is expected to be close to 25 ppm based on the minimal changes observed at 25 ppm.

Table B35. Incidence (%) of Hepatic, Testicular and Mammary Tumors in Rats Exposed to DMF.

Findings	Sex	DMF (ppm)			
		0	25	100	400
Primary hepatic tumors					

Findings	Sex	DMF (ppm)			
		0	25	100	400
Hepatocellular adenoma	(M)[a]	2 (1/57)[b]	2 (1/59)	5 (3/58)	3 (2/60)
	(F)	0 (0/60)	2 (1/59)	0 (0/59)	0 (0/60)
Hepatocellular carcinoma	(M)	0 (0/57)	0 (0/59)	0 (0/58)	2 (1/60)
	(F)	0 (0/57)	0 (0/59)	0 (0/59)	0 (0/59)
Primary testicular tumors					
Testicular interstitial cell adenomas	(M)	9 (5/57)	7 (3/44)[c]	0 (0/41)[c]	10 (6/60)
Testicular mesothelioma	(M)	0 (0/57)	0 (0/44)[c]	0 (0/44)[c]	2 (1/60)
Primary mammary tumors					
Fibroadenoma	(M)	2 (1/44)	8 (3/37)[c]	11 (4/38)[c]	3 (1/32)
Adenomad	(F)	55 (33/60)	64 (34/53)[c]	63 (34/54)[c]	37(23/62)*
	(F)	2 (1/60)	2 (1/53)	4 (2/54)	2 (1/62)

[a]M, male; F, female.
[b]Numerator represents number of tumors, and the denominator represents number of tissues examined.
[c]For the 25 and 100 ppm concentrations, non-target organ tissues (such as testes and mammary gland) were examined only in animals which died prior to scheduled sacrifice or had grossly observable lesions.
[d]This lesion was not observed in males.
*statistically significant at $p < 0.05$.

Table B36. Incidence (%) of Hepatic, Testicular and Mammary Tumors in Mice Exposed to DMF.

Findings	Sex	DMF (ppm)			
		0	25	100	400
Primary hepatic tumors					
Hepatocellular adenomas	(M)[a]	22 (13/60)[b]	18 (11/62)	18 (11/60)	19 (11/59)
	(F)	0 (0/61)	2 (1/63)	3 (2/61)	2 (1/63)
Hemangioma	(M)	2 (1/60)	0 (0/62)	0 (0/60)	2 (1/59)
	(F)	0 (0/61)	0 (0/63)	2 (1/61)	2 (1/63)
Hepatocellular carcinoma[c]	(M)	0 (0/60)	2 (1/62)	7 (4/60)	3 (2/59)
Hemangiosarcoma[c]	(M)	0 (0/60)	0 (0/62)	2 (1/60)	3 (2/59)
Primary testicular tumors					
Interstitial cell adenoma	(M)	2 (1/59)	0 (0/22)[d]	0 (0/25)[d]	0 (0/56)
Primary mammary tumors					
Adenocarcinoma[e]	(F)	3 (2/62)	4 (1/26)d	12 (3/26)[d]	0 (0/58)

[a]M, male; F, female.
[b]Numerator represents number of tumors, and the denominator represents number of tissues examined.
[c]This lesion was not observed in females
[d] For the 25 and 100 ppm concentrations, nontarget organ tissue (such as testes and mammary gland) were examined only in animals which died prior to scheduled sacrifice or had grossly observable lesions.
[e] This lesion was not observed in males.
*statistically significant at $p < 0.05$.

Senoh et al., 2004

Carcinogenicity and chronic toxicity of DMF were examined by inhalation exposure of groups of 50

rats and 50 mice of both sexes to DMF vapour at a concentration of 0, 200, 400 or 800 ppm (v/v) for 6 h/d, 5 d/wk, for 104 wk. In rats, incidences of hepatocellular adenomas and carcinomas significantly increased in the 400 and 800 ppm-exposed groups and in the 800 ppm-exposed group, respectively (Table B37). The hepatocellular adenoma did not increase significantly in the 400 ppm exposed female rats, but its incidence exceeded a range of historical control data in the Japan Bioassay Research Center (JBRC). In mice, incidences of hepatocellular adenomas and carcinomas significantly increased in all the DMF-exposed groups (Table B38). Incidence of hepatoblastomas significantly increased in the 200 and 400 ppm-exposed male mice, and 4 cases of hepatoblastomas in the 400 ppm-exposed female mice and the 800 ppm-exposed male mice exceeded the range of historical control data of the JBRC. Incidences of altered cell foci increased in the liver of exposed rats and mice in an exposure concentration-related manner, and those foci were causally related to the hepatocellular tumors. Liver weights increased in both rats and mice exposed to DMF at 200 ppm and above. Increased levels of γ-GTP, ALT, AST and total bilirubin in exposed rats of both sexes and AST and ALT in exposed mice of both sexes were noted. It was concluded that 2-year inhalation exposure to DMF increased incidences of hepatocellular adenomas and carcinomas in rats and incidences of hepatocellular adenomas, carcinomas and hepatoblastomas in mice, and that hepatocarcinogenicity of DMF was more potent in mice than in rats. The exposure to 800 ppm exceeded the MTD (maximum tolerated dose) only for female rats, but the incidence of hepatocellular adenomas in the 400 ppm-exposed female rats was increased to more than the upper range of the JBRC historical data.
The doses selected in this study exceeded the MTD, which was exacerbated by probable exposure to an aerosol during atmosphere generation. The selection of test system used in these studies may have contributed to increased tumor incidence observed (see Conclusion).

Table B37. Incidences of neoplastic and non-neoplastic liver lesions and first appearance of hepatocellular tumors in the rats exposed to DMF vapour at different concentrations.

Group	Male				Peto	Female				Peto
	Control	200 ppm	400 ppm	800 ppm		Control	200 ppm	400 ppm	800 ppm	
No. of animals examined	50	50	50	50		49 a)	50	50	50	
Neoplastic lesions										
Hepatocellular adenoma	1	3	13**	20**	↑↑	1	1	6	16**	↑↑
Hepatocellular carcinoma	0	1	0	24**	↑↑	0	0	0	5*	↑↑
Hepatocellular tumors b)	1	4	13**	33**	↑↑	1	1	6	19**	↑↑
Pre-neoplastic lesions										
Altered cell foci										
Clear cell foci	11	21	35**	40**		3	23**	33**	33**	
Eosinophilic cell foci	13	14	34**	40**		0	4	10**	20**	
Basophilic cell foci	24	26	29	42**		23	27	15	29	
Mixed cell foci	0	0	1	6*		0	0	0	1	
Vacuolated cell foci	6	0*	7	16*		0	0	1	3	
Spongiosis hepatis	4	21**	26**	24**		0	0	0	2	
Non-neoplastic lesions										
Necrosis:centrilobular	1	5	0	5		0	3	2	13**	
				(3)					(13)	
Necrosis:focal	0	3	7*	2		0	2	1	3	
Necrosis:single cells	0	0	0	0		0	0	1	0	
No. of dead or moribund animals bearing hepatocellular tumors	0	0	2	5		0	1	1	1	
First appearance of hepatocellular tumor (wk)			91	97			104	104	101	

Group	Male				Peto	Female				Peto
	Control	200 ppm	400 ppm	800 ppm		Control	200 ppm	400 ppm	800 ppm	
No. of animals bearing hepatocellular tumors surviving at time of terminal necropsy c)	1	4	11	28		1	0	5	18	

Significant difference; *: p<0.05, **: p<0.01 by Fisher Exact Test.
↑: p<0.05, ↑↑: p<0.01 by Peto's Test (Peto)
( ): Number of rats which died of centrilobular necrosis within the first 13 wk (for males) or 21 wk (for females).
a: Number of female rat examined was 49 instead of 50, because one rat accidentally died.
b: The hepatocellular tumors include hepatocellular adenoma and hepatocellular carcinoma.
c: Terminal necropsy was started at the 105th wk.

Table B38. Incidences of neoplastic and non-neoplastic liver lesions and first appearance of hepatocellular tumors in the mice exposed to DMF vapour at different concentrations.

Group	Male				Peto	Female				Peto
	Control	200 ppm	400 ppm	800 ppm		Control	200 ppm	400 ppm	800 ppm	
No. of animals examined	50	50	49 a)	50		49 a)	50	50	49 a)	
Neoplastic lesions										
Hepatocellular adenoma	6	36**	41**	41**	↑↑	1	42**	47**	48**	↑↑
Hepatocellular carcinoma	2	12**	16**	16**	↑↑	3	25**	32**	35**	↑↑
Hepatoblastoma	0	13**	7**	4		0	0	4	0	
Hepatocellular tumors b)	8	42**	46**	44**	↑↑	3	45**	49**	49**	↑↑
Pre-neoplastic lesions										
Altered cell foci										
Clear cell foci	4	21**	13**	17**		3	7	4	2	
Eosinophilic cell foci	1	38**	41**	42**		1	43**	43**	48**	
Non-neoplastic lesions										
Centrilobular hypertrophy	0	39**	41**	48**		2	11*	5	16**	
Nuclear atypia: centrilobular	0	33**	42**	45**		2	7	3	16**	
Necrosis: focal	8	17	9	0*		2	2	3	2	
Necrosis: single cell	12	38**	43**	48**		22	13	6**	19	
Inflammatory cell nest	15	37**	42**	48**		24	13*	4**	19	
No. of dead or moribund animals bearing hepatocellular tumors	2	11	11	5		0	16	28	27	
First appearance of hepatocellular tumor (wk)	97	84	67	78			62	68	52	
No. of the animals bearing hepatocellular tumors survived at the time of terminal necropsy c)	6	31	35	39		3	29	21	22	

Significant difference; *: p<0.05, **: p<0.01 by Fisher Exact Test.
↑: p<0.05, ↑↑: p<0.01 by Peto's Test (Peto)
a: Number of mice examined was 49 instead of 50, because one mouse accidentally died.
b: The hepatocellular tumors include hepatocellular adenoma, hepatocellular carcinoma and hepatoblastoma.
c: Terminal necropsy was started at the 105th wk.

Ohbayashi et al., 2009

Hepatocarcinogenic effect of combined: an inhalation and oral exposure of rats to DMF was examined. A group of 50 male F344 rats, 6 -week old, was exposed by inhalation to 0 (clean air), 200 or 400 ppm (v/v) of DMF vapour-containing air for 6 h/day and 5 days /week during a 104 week period, and each inhalation group was given *ad libitum* DMF-formulated drinking water at 0, 800 or 1600 (w/w) for 104 weeks. Incidences of hepatocellular adenomas and carcinomas and their combined incidences were significantly increased in the combined-exposure groups compared with the untreated control group or each of the inhalation-alone and oral-alone groups (Table B39). Incidences of hepatocellular adenomas and carcinomas induced by the combined exposures were greater than the sum of the two incidences of the hepatocellular adenomas and carcinomas induced by the single-route exposures through inhalation and ingestion. The combined exposures enhanced tumor malignancy. The hepatocarcinogenic effect of the combined exposures is greater than the effect that would be expected under assumption that two effects of single-route exposures through inhalation and drinking are additive (possibly synergistic). The doses selected in this study exceeded the MTD, which was exacerbated by probable exposure to an aerosol during atmosphere generation. The selection of test system used in these studies may have contributed to increased tumor incidence observed (see Conclusion).

Table B39. Number of male rats bearing hepatocellular tumors following combined inhalation and oral exposures or single-route exposures to DMF.

Inhalation (ppm)	**0**			**200**			**400**		
Drinking water (ppm)	**0**	**800**	**1600**	**0**	**800**	**1600**	**0**	**800**	**1600**
Total estimated amount of DMF uptake (mg/kg/day)	0	(44)	(82)	(121)	(165)	(205)	(242)	(289)	(338)
Number of animals examined	50	50	50	50	50	50	50	50	50
Number of animals dead or found in a moribund state	9	16	10	14	14	9	13	7	12
Hepatocellular adenoma	1	6^{a}	8^{a}	15^{a}	$28^{a,b,c}$	$45^{a,b,c}$	26^{a}	$43^{a,b,c}$	$46^{a,b,c}$
	0	(2)	(2)	(2)	(1)	(4)	(3)	(3)	(9)
Hepatocellular carcinoma	0	0	4^{a}	1	$6^{a,b,c}$	$14^{a,b,c}$	2	$12^{a,b,c}$	$14^{a,b,c}$
	0	0	0	0	0	(1)	0	(1)	(2)
Hepatocellular adenoma + carcinoma	1	6^{a}	12^{a}	16^{a}	$30^{a,b,c}$	$46^{a,b,c}$	26^{a}	$45^{a,b,c}$	$47^{a,b,c}$
	0	(2)	(2)	(2)	(1)	(5)	(3)	(4)	(9)
Poorly differentiated, hepatocellular carcinoma	0	0	1	0	$5^{a,b,c}$	$5^{a,c}$	2	$9^{a,b,c}$	$9^{a,b,c}$
	0	0	0	0	0	0	0	0	(2)
Number of animals died of liver tumors	0	0	0	0	0	2	1	4	4

[a, b and c]: significantly different from the untreated control group, the each oral-alone group and each inhalation-alone group with matching concentrations, respectively, at $p < 0.05$ by chi-square test.

Parenthesized values indicate number of male rats dead and found in a moribund state, bearing hepatocellular tumors on the basis of histopathological examination. Number of animals died of liver tumors was based on the primary cause of deaths diagnosed on the basis of macroscopic and microscopic findings.

Summary of old studies (OECD SIDS, 2004)

In old studies of different duration with rats, mice, Syrian hamster treated with different dose levels administered in drinking water or by i.p. and s.c. routes, no tumors were observed. However, at the very high dose (4000 mg/kg bw), administered by i.p. route to rats during 10 weeks, multiple tumors (adenocarcinoma, sarcoma, leyomyoma, carcinoma of the rectum, phaeochromocytoma of the adrenal medulla, embryonal cell like tumors of the testis and numerous benign tumors) irregular and partial liver cell necrosis and ulceration of the intestinal mucosa occurred. An untreated control group with 14 male and 14 female animals run in parallel. The DMF-treated animals served as solvent-control group for a group of animals treated with aflatoxine dissolved in DMF. In both groups comparable tumor incidences occurred. The validity of the investigation is limited due to assessments of the performing institute itself (Clayson D.B.; 1977, cited in OECD SIDS) and assessments of external sites. The tumor incidences given in the publications are varying.

Human data

Ducatmann et al., 1986 (adopted from Health Canada, 1999)

Three cases of testicular germ cell tumours that occurred during 1981-83 among 153 white men who repaired the exterior surfaces and electrical components of F4 Phantom jets in the United States were reported, which led to surveys of two other repair shops at different locations, one in which F4 Phantom jets were repaired and one where other types of aircraft were repaired. Four of 680 workers in the F4 Phantom shop had testicular germ cell cancers (approximately one expected) diagnosed during 1970-83. No cases were reported in the other facility. All seven men had long histories in aircraft repair; although there were many common exposures to solvents in the three facilities, the only one identified as unique to the F4 Phantom jet aircraft repair facilities was to a solvent mixture containing 80 % DMF (20 % unspecified). Three of the cases had been exposed to this mixture with certainty, and three had probably been exposed. Of the seven cases, five were seminomas and two were embryonal cell carcinomas.

Calvert et al., 1990

The National Institute for Occupational Safety and Health (NIOSH) conducted a standardised incidence ratio study (SIR) of finishing department workers at the tannery. The cohort of the study comprised 80 persons who had worked in one tannery in the years 1975 – 1987. The incidence (three observed cases) of testis cancer was compared with the expected value determined with the data of the New York State cancer registry. The resulting standardized incidence ratio 40.5 (95 % CI 8.1–118.4) was significantly increased. However, no additional cancers were reported in a screening effort in June 1989 undertaken to identify additional testicular cancers in 51 of the 83 workers at the leather tannery where the three cases were reported.
This investigation confirmed an excess of testicular cancer at a tannery. This adds to concerns about the carcinogenicity of DMF but conclusions should be tempered by a lack of detailed information about exposure to DMF and because of coexistent exposures to other chemicals at the tannery.

Chen et al., 1988a (adopted from Health Canada, 1999)

In the cohort study of 3859 actively employed workers with potential exposure to DMF and to DMF and acrylonitrile (ACN) in a fibre production facility, the incidences of cancer of the buccal cavity/pharynx, lung, prostate, stomach, nervous system and bladder were considered in relation to level of and, for some tumours, duration of exposure and were compared with company and national rates. Level of exposure was classified as low (approximately <10 ppm [<30 mg/m³]), moderate (sometimes above 10 ppm [30 mg/m³]) or high, although quantitative data were not reported. Women

were excluded from analyses because of the small numbers. When compared with company and national rates, there was no increase in the incidence of testicular cancer in 2530 actively employed workers exposed to DMF only. When the data from this cohort were grouped with data from 1329 workers exposed to both DMF and ACN, there was only one case of testicular cancer, compared with 1.7 expected (confidence intervals [CI] not reported). Further, there was a significant increase in prostate cancer (10 observed vs. 5.1 expected from company rates and 5.2 expected from national rates; $p < 0.10$ for both comparisons) in the 3859 workers exposed either to DMF or to both DMF and ACN. However, when only DMF-exposed workers (2530) were considered, the standardized incidence rate (SIR) (4 observed vs. 2.4 expected from company rates) was not significant. Chen et al. (1988a) also reported a significant increase in the incidence of cancer of the buccal cavity/pharynx (9 observed vs. 1.6 expected from company rates; $p < 0.10$) in the 2530 DMF-exposed workers (confidence intervals not reported). When combined with data from 1329 workers exposed to both DMF and ACN, the increase (11 observed) was significant when compared with the company rate (3.2 expected, $p < 0.01$), but not when compared with national rates (6.6 expected). There was no relation to either level or duration of exposure. All cases were heavy, long-term smokers.

Chen et al., 1988b

Excess mortality from ischemic heart disease in DMF-exposed workers in a U.S. ACN fibre plant was observed in a historical cohort study. Between 1950 and 1982, there were 62 deaths due to ischemic heart disease (40.3 expected from company rates; $p < 0.01$). The increase was not significant in comparison with the state (South Carolina) rates. A similar observation was made for a second group of 1329 employees at the plant who were potentially exposed to both DMF and ACN (65 deaths observed, 48.3 expected from company rates; $p < 0.05$). However, the rate was not significantly higher than either state or national rates. Lifestyle factors were suggested to be more likely causes than exposure to DMF.

Table B40. Selected Causes of Death, 1950 to 1982, DMF-only Cohort, Based on Du Pont Company Rates.

	Wage		Salary		Total	
	Obs	Exp	Obs	Exp	Obs	Exp
All causes	184	115.2*	41	45.0	225	160.2*
All malignant neoplasms	29	27.1	9	13.0	38	40.1
Buccal cavity and pharynx	1	0.6	1	0.2	2	0.8
Digestive	6	6.5	1	3.4	7	9.9
Lung	14	9.9	5	3.6	19	13.5
Nervous system	2	1.4	1	0.7	3	2.1
All lymphatic	4	3.5	0	1.7	4	5.2
All other	2	5.2	1	3.0	3	8.2
Ischemic heart disease	62	40.3*	15	17.0	77	57.3**
Cerebrovascular disease	5	5.5	4	2.2	9	7.7
Diseases of digestive system	8	3.4**	0	1.5	8	4.9
External causes	44	23.9*	2	4.7	46	28.6*

* Significantly greater than expected, $P < 0.01$ (two-tailed)

** Significantly greater than expected, $P < 0.05$ (two-tailed)

Table B41. Selected Causes of Death, 1950 to 1982, Nonexposed Cohort, Based on Du Pont Company Rates.

	Wage		Salary		Total	
	Obs	Exp	Obs	Exp	Obs	Exp

	Wage		Salary		Total	
	Obs	Exp	Obs	Exp	Obs	Exp
All causes	43	26.9*	35	34.6	78	61.5
All malignant neoplasms	7	5.6	8	9.6	15	15.2
Ischemic heart disease	11	8.2	8	13.3	19	21.5
External causes	14	7.7**	10	3.4*	24	11.1*

* Significantly greater than expected, P < 0.01 (two-tailed)

** Significantly greater than expected, P < 0.10 (two-tailed)

Levin et al., 1987

Case reports from 1987 describe testis cancer in three leather tannery workers. They were exposed for 8 to 14 years to a number of chemicals including dimethylformamide and a wide range of dyes and solvents such as testicular toxins as 2-ethoxyethanol and 2-ethoxyethanol acetate. Exposure took place by inhalation of aerosols and by skin contact. Two men had an embryonal cell carcinoma, the third an embryonal cell carcinoma and a seminoma.

Walrath et al., 1989

A case-control study in 4 factories producing and processing dimethylformamide with an average of 8724 male employees per year described for the years 1956 to 1985 a total of 39 oral cavity and throat carcinomas, 6 liver tumours, 43 prostate carcinomas, 11 testis tumours and 38 malignant melanomas. There was no increase in the incidence of cancer of the testis (odds ratio = 0.91; 95 % CI = 0.1-8.6; observed number of cases = 11; Health Canada, 1999). The odds ratio for prostate cancer was not significantly elevated (1.48; 95 % CI = 0.59-3.74; 43 cases; Health Canada, 1999). When analyses were carried out separately for each of the four plants, an increased incidence was observed only at one plant, where the exposure to DMF was lower and the number of cases was fewer than at the other plants. Adjustment for assumed latency period did not alter the odds ratio. There was no increase in risk of cancer of the buccal cavity/ pharynx (odds ratio = 0.89; 90 % CI = 0.35-2.29, 39 cases; Health Canada, 1999). There was no relationship with duration of exposure. Potential exposure to DMF was classified as low or moderate based on job title/work area combinations and monitoring data (Table B42).
Summary analyses over all plants combined show no statistically significant association between ever having been exposed to DMF and subsequent development of cancers of the buccal cavity and pharynx, liver, malignant melanoma, prostate, and testis. Furthermore, it is assumed that other occupational, life-style, and hereditary risk factors may have been acting as confounders in this study, spuriously inflating the observed odds ratios or masking a causal association between DMF exposure and disease.

Table B42. Criteria for Ranking of Job Exposures by Geometric Mean and 95th Percentile.

	Measured Exposure-Geometric Mean, ppm	Best Estimate* of the 95th Percentile, ppm	Rank
DMF in air	0	0	0-None
	<1.0	<5.0	P-Present, but not analytically detectable** for below 1 ppm
	1.0-<2.0	5.0-<10.0	1-Low
	2.0-<10.0	10.0-<50.0	2-Moderate
	10.0+	50.0+	3-High
MMF in urine	0	0	0-None
	<1.0	<5.0	P-Present, but not

	Measured Exposure-Geometric Mean, ppm	Best Estimate* of the 95th Percentile, ppm	Rank
			analytically detectable** or below 1 ppm
	1.0-<5.0	5.0-<25.0	1-Low
	5.0-<20.0	25.0-<100.0	2-Moderate
	20.0+	100.0+	3-High

* Best estimate of the 95th percentile value is 5 times the geometric mean.

** Until 1985, minimum level of detection of both DMF and MMF was 1.0 ppm.

Conclusion on carcinogenicity

The conclusion on carcinogenicity potential of DMF as stated in OECD SIDS (2004) and registration dossier is given below. The Dossier submitter supports the conclusion on carcinogenicity.
DMF was studied for its carcinogenicity potential in three inhalation studies, which provides contraversial results for this endpoint. No increased incidence of hepatic tumors occurred in the 2-year inhalation study in rats and mice (Malley et al., 2004), while during another 2 year-inhalation study to DMF vapour increased incidences of benign and malignant neoplasms in two rodent species, hepatocellular adenomas and carcinomas in F344 rats and hepatocellular adenomas and carcinomas and hepatoblastomas in BDF1 mice were observed (Senoh et al., 2004). Ohbayashi et al. (2009) confirmed the findings of Senoh et al. (2004).

However, a critical evaluation of the manuscripts revealed that technical aspects of the Senoh et al (2004) study substantially deviated from the OECD 451 guideline. Therefore, the Senoh et al (2004) study cannot be used for hazard assessment or risk assessment. In this study, the doses selected exceeded the maximum tolerated dose (MTD), which was exacerbated by probable exposure to an aerosol during atmosphere generation. In addition, the selection of test system used for this study may have contributed to increased tumor incidence observed. The study is devalidated based on exceeding the MTD and on the technical aspects of atmosphere generation and analysis and test system selection.

Reason for devalidation of Senoh et al., 2004 study:

Exposure concentrations associated with tumors exceeded the MTD.

Senoh et al, 2004. acknowledge and discuss the concerns that are generated by the excessive toxicity apparent in their observations. Although they acknowledge that the mortality levels, decreased body weight gain and pervasive liver damage would normally establish that the Maximum Tolerated Dose (MTD) has been exceeded, the authors argue that the MTD was only exceeded in the female rats, and only at the highest exposure concentration of 800 ppm. Senoh et al (2004) concluded that the liver necrosis was triggered by the oncogenic effects of DMF and not the general, targeted hepatocellular toxicity of DMF. However, globally recognized testing guidelines recognize that persistent hepatocellular cytotoxicity results in eventual neoplasia and provides the following guidance for selection of dose levels in chronic toxicity or oncogencity studies:

> *"With regard to the appropriateness of the high dose, an adequate high dose would generally be one that produces some toxic effects without unduly affecting mortality from effects other than cancer or producing significant adverse effects on the nutrition and health of the test animals (OECD, 1981, NRC 1993)."*

EPA guidelines on the conduct and interpretation of carcinogenicity studies (2005) provide further guidance and cite the following examples of excessive toxicity:

> *"significant increases in mortality from effects other than cancer generally indicate that an adequate high dose has been exceeded.*

> *Other signs of treatment-related toxicity associated with an excessive high dose may include (a) significant reduction of body weight gain (e.g., greater than 10 %), (b) significant increases in abnormal behavioral and clinical signs, (c) significant changes in hematology or clinical chemistry, (d) saturation of absorption and detoxification mechanisms, or (e) marked changes in organ weight, morphology, and histopathology."*

All of these indicators of signs of exceeding the MTD were present in Senoh et al 2004. for rats at the two highest concentrations (400 and 800 ppm), and at all concentrations for mice. In mice, Senoh et al 2004 reported significant adverse effects on the liver at all exposure concentrations, in both sexes and with no dose response. All three exposure concentrations resulted in significant but flat increases in relative liver weight, and dramatic increases in hepatic damage based on serum chemistry values and histological findings. In rats, similar hepatic distress was evident for the two highest dosing levels based on increased relative liver size, increased blood serum markers, and increased incidences of severe hepatic effects such as hepatic spongiosis and focal necrosis. Neoplastic findings in males were recorded only in the presence of decreases in body weight gains of 13 % and 24 % at 400 and 800 ppm, respectively; and in the female rat, an increase in tumors was seen only at a concentration associated with a 29 % decrease in body weight, and 24 % lower survival, compared to controls.

All experimentation on DMF illustrates that the liver is the target organ for toxicity, and saturation of DMF metabolism leads to pervasive hepatocellular necrosis. (IARC, 1999.) Furthermore, Hundley, et al (1993) demonstrated that metabolism of DMF in rats and mice was saturated at vapour concentrations greater than 250 ppm, further confirming the conclusion that the MTD was exceeded in Senoh et al (2004). In addition, DMF appears to affect the mouse liver more severely, apparently due to the higher plasma levels of DMF compared with the rat. The plasma Area Under the Curve (AUC) increased 29-fold in the mouse as DMF concentrations increased from 250 to 500 ppm, compared to an 8-fold increase in AUC for rats over this concentration range. (Hundley et al, 1993).

For both the rat and mouse data generated by Senoh et al (2004), the findings do not support a conclusion that DMF has a direct carcinogenic potential. Only highly compromised tissues, at the end of continuous chronic exposures, were prone to produce neoplasia amongst the secondary consequences of these extreme assaults on the liver.

Atmosphere generation techniques resulted in higher exposure than acknowledged in the study report.

DMF is challenging to vapourize in inhalation chambers for extended periods, due to its relatively low vapour pressure. The low vapour pressure at room temperature (3.7 mm Hg @ 25ºC) can result in aerosol formation unless the airflow through the chamber is sufficiently high enough to prevent formation of aerosol droplets. It is likely that the 800 ppm concentration claimed by Senoh et al (2004) was a vapour/aerosol mixture based on their reported chamber air exchange rate in Senoh et al (2004) that was lowered from 12 to 6 air exchanges per hour during the 6 hour exposure periods (for reasons not explained in the study). The OECD testing guidelines for inhalation studies specify that a "dynamic air flow rate of 12 to 15 air changes per hour [is necessary] to ensure adequate oxygen concentration of 19 percent and an evenly distributed exposure atmosphere." The method of atmosphere generation used for the chronic study was also used and described in the Senoh et al (2003) subchronic study. Senoh et al (2003) described their atmosphere generation method as "spraying liquid DMF into the air space of the solvent chamber, further diluting the vapour with clean air." This technique, as described, likely resulted in the generation of aerosol particulates. The analytical method used by Senoh et al (2003, 2004). to verify exposure concentrations would not differentiate DMF vapour from aerosol. Aerosolization of DMF would result in significant dermal and/or oral exposures (from grooming behavior) in addition to the intended inhalation exposure.

The likelihood that the procedures used by Senoh et al (2004) enhanced the generation of DMF aerosols in the experimental chambers is consistent with the striking difference between the results of Malley et al (1994) and Senoh et al (2004) at similar targeted exposure concentrations. DMF is well absorbed through the skin, and aerosol deposition on the animals during whole body exposure would be expected

to result in much higher internal doses of DMF from grooming (oral exposure) and dermal absorption than anticipated from the air levels measured in the exposure chambers.

Test animal strains used by Senoh et al, 2004 modified the potential sensitivity to DMF.

Senoh et al (2004) used F 344/DuCrj rats and Crj:BDF_1 mice. The mouse strains used by Senoh et al (2004) have been shown to have differential sensitivity in the mutations caused by known genotoxic hepatocarcinogens compared to the standard mouse strains used in carcinogenicity studies, including the B6C3F1, Balb/c, and C3H mouse strains (Kushida et al., 2006). The use of these sensitive strains exacerbated the response in the liver, causing excessive damage, even at low dosing levels.

In addition, the spontaneous tumor profile of the rat and mouse strains used by Senoh et al 2004 has not been evaluated. OECD Guideline 451 provides the following guidance on selection of the species and strain for carcinogenicity studies:

> "*The use of inbred strains has the advantage of the availability of animals with known characteristics, such as an average life span and a predictable spontaneous tumour rate. ...A good knowledge of the tumour profile of the animal strain throughout the life span is highly desirable in order to evaluate the results of experiments in a proper way. Preference should be given to strains with a low incidence of spontaneous tumours."* (OECD 1981)

The Malley et al (1994) study and the Senoh et al (2004) studies are very similar in structure, particularly in the following parameters:

- Test animals (both rats and mice);
- Route of exposure (inhalation);
- Frequency of exposure (5 days per week, 6 hours per day);
- Clinical pathology evaluations, and
- Tissues examined and collected (full range).

Nevertheless, the two studies differed in several key elements:

- Exposure concentrations: Senoh et al (2004) used a high concentration of 800 ppm, exceeding the MTD, compared to a high concentration of 400 ppm in Malley et al (1994).
- The atmosphere generation techniques used by Senoh et al (2004) probably produced aerosolized particles that further increased exposure and were not detected due to the method of atmosphere analyses.
- The mouse strain used by Senoh et al (2004) may be more sensitive to hepatoxins than the standard strain used in Malley et al (1994).

These differences resulted in significantly different levels of toxicity to the target tissue, the liver, as demonstrated by extensive hepatocellular damage, ultimately leading to hepatocellular adenomas and carcinomas. Although Senoh et al (2004) acknowledged that the MTD was exceeded in female rats; they did not adequately address the implications of that flaw. Specifically, Senoh et al (2004) fail to account for the fact that the male rats showed oncogenicity only at the two concentrations associated with significant liver damage and decreases in body weight gain. Since the exposure concentrations in the Senoh et al. (2004) significantly exceeded the MTD, and the method of analyses used would not have detected the presence of an aerosol in the exposure chamber, rendering the quantification of the exposure concentrations unusable, the Senoh et al. (2004) study cannot be used as a key study for hazard identification or risk assessment purposes.

Similarly, the studies by Ohbayashi et al (2008, 2009) also cannot be used as key studies for classification of carcinogenicity due to exceeding the MTD.

These studies are scored as a K3 due to exceeding the MTD. In addition, the results of Ohbayashi et al (2009) confirm that the excessive liver toxicity reported in Senoh et al (2004) were due to a combined inhalation exposure and oral/dermal exposure resulting from aerosol deposition on the skin and fur.
DMF should not be classified as a carcinogen (CLP Cat 1a or 1b or Cat 2) due to the following reasons:

• DMF was not oncogenic at doses that don't exceed metabolic saturation: Male and female rats (Crl:CD BR) and mice (Crl:CD-1 (ICR)BR) were exposed by inhalation to DMF for 6 hours per day, 5 days per week for 18 months (mice) or 2 years (rats) at concentrations of 0, 25, 100, or 400 ppm according to U.S. Environmental Protection Agency TSCA 799.9430 Guidelines, and OECD 453 Guidelines (Malley et al, 1994). Dosing levels were verified by gas chromatography, and the authors established that aerosolized particles were not present, so that inhalation was the only significant route of exposure. There were no effects on clinical observations or survival in either species. Body weights of rats exposed to 100 and 400 ppm were reduced. Conversely, body weights were increased in mice exposed at 400 ppm. No hematologic changes were observed in either species. The hepatic enzyme sorbitol dehydrogenase activity was increased in rats exposed at 100 and 400 ppm. For both species, microscopic compound-related changes were only observed in the liver. In rats, exposure at 100 or 400 ppm caused an increase in the ratio of liver weight to body weight, hepatocellular hypertrophy, pigment accumulation, and single cell necrosis. In mice, exposure to DMF at 100 or 400 ppm caused an increase in the ratio of liver weight to body weight, hepatocellular hypertrophy, and pigment accumulation. Increased hepatic single cell necrosis was observed at 25, 100, and 400 ppm. Varying types of non-neoplastic hepatic foci of alteration were increased in mice at 100 ppm and above.

This was confirmed also by multiple weight of evidence originated from the old studies reported in OECD SIDS report (2004). The tumors were observed in rats by repeated exposures to only very high dose (4000 mg/kg bw) of DMF (Clayson D.B.; 1977, cited in OECD SIDS, 2004)

• DMF is not genotoxic: DMF was negative in the majority of genetic toxicity tests conducted including *in vivo* dominant lethal assays in rats exposed by inhalation and in mice exposed dermally or by intraperitoneal injection (Lewis 1979; Monsanto 1972; BASF 1976). In addition, DMF exposure did not alter the frequency of sister chromatid exchanges in exposed workers. (Cheng et al., 1999). Single instances of positive results from an unscheduled DNA synthesis study (Williams, 1977), a micronucleus study (Ye, 1987), and chromosome aberration study (Koudela and Spazier 1979), were not repeatable in multiple tests performed by other laboratories. (IARC, 1999). IARC reviewed this extensive body of data and concluded that DMF is consistently negative for genotoxicity in well controlled studies.

• DMF was not oncogenic in well conducted studies of occupationally exposed workers: Two studies describing the cancer incidence and mortality in a cohort of 5,005 workers at an acrylic fiber plant with 3,859 workers exposed to DMF were published by Chen, et al (1988a, b.). One case of testicular cancer, and 11 cases of buccal/pharynx cancer with a significantly elevated SIR for 9 cases in 2,350 workers exposed to DMF-only; however, only one case was observed in the 1,329 workers exposed to DMF and acrylonitrile. Moreover, the risk of buccal/pharynx cancer did not increase with increasing exposure level or duration of exposure to DMF as detailed in the Chen et al. manuscript. Finally, the authors observed that all 11 cases of buccal/pharynx cancer in the cohort were heavy smokers for a duration of at least twenty years.

In addition, a case-control study was conducted at four plants where DMF was produced or used (Walrath, et al. 1989). This study assessed exposure to DMF for eleven cases of testicular cancer and cases of other rare cancers including buccal/pharynx (39 cases), liver (6 cases), melanoma (38 cases), and prostate (43 cases). Two control subjects were matched to each cancer case based on sex, birth year, plant, and payroll class (wage or salary). The authors conclude that there is no causal relationship between exposure to DMF and any of the cancers studied. Although they identified limitations of low statistical power due to the small number of cancer cases and the inability to study persons no longer employed at the 4 facilities at the time of the investigation, it is noteworthy that this study includes a greater number of cancer cases than other case-control studies cited in the literature, and it also includes documented exposure to DMF, which were not documented in previously published case-control studies.

GHS classification for carcinogenicity specifically addresses using a weight of evidence approach, and consideration of additional factors such as:

"The possibility of a confounding effect of excessive toxicity at test doses." (Globally Harmonized System of Classification and Labeling of Chemicals (GHS) 2009)".

EPA 2005 similarly states that results from studies in which tumors are observed only at excessive doses should not be used for assessing human hazard and risk:

In conclusion, the studies of Senoh et al (2004), and Ohbayashi et al (2008, 2009) cannot be used for classification due to excessive toxicity, and technical difficulties with atmosphere generation and analysis, and animal strain selection. Based on the study by Malley et al (1994), as well as the absence of genotoxicity, and no evidence of increased tumors in exposed workers, DMF should be classified as not carcinogenic.

Table B43. Point of departures for DNEL derivation for systemic chronic toxicity.

POD for DNEL derivation (endpoint)	Species and duration	NOAEC ppm (mg/m³)	Toxicological endpoint	Reference
Systemic				
Inhalation	Rats, mice, 2-years	25 ppm (80 mg/m³) 400 ppm (1210 mg/m³) for oncogenicity	Decreased body weights, clinical chemistry changes, liver injury; no increased incidence in tumors.	Malley et al., 1994

B.5.9. Toxicity for reproduction

The information of toxicity to reproduction was gathered from the registration dossier and the OECD SIDS (2004). Study descriptions and NOAELs/LOAELs were taken from the registration dossier, unless stated otherwise.

Fertility

Oral

In a continuous breeding study CD-1 mice were treated orally with DMF in the drinking water at doses of 1000, 4000 and 7000 ppm (about 219, 820 and 1455 mg/kg bw/day) (Fail et al., 1998). The maximal tolerated dose (MTD) for generalized toxicity was 1000 ppm for the F0 and the F1 generation, thus a systemic NOAEL could not be determined. Reproductive toxicity was observed in the mid and high dose groups represented by reduced fertility. In the Table B44 altered measures of fertility and fecundity of F0 mice are presented. At 7000 ppm DMF, fertility was reduced in the first litter to 90 %, compared to 100 % in controls. Over time, this treatment-related effect increased. By the final litter, fertility was further reduced to 55 % at 7000 ppm. By this time, reduced fertility was also noted at 4000 ppm. For pairs exposed at 4000 ppm or greater, the average number of litters per pair, average litter size, proportion of pups born alive, and average pup weight were reduced compared to control pairs. DMF treatment had no effect on these parameters in the 1000 ppm group.

Table B44. Fertility and reproductive performance of F0 mating pairs.

Dimethylformamide in water (ppm)				
	0	**1000**	**4000**	**7000**
No. breeding pairs	38	20	20	20
Percent fertile (first litter)[a]	100†	100	100	90*

Percent fertile (final litter)	92†	95	70*	55*
Cumulative days to litter (first litter)[b]	21.7 ± 3 (38)	24.5 ± 1.1 (19)	28.1 ± 4.2 (20)	23.1 ± 1.9 (18)
Cumulative days to litter (final litter)[b]	103 ± 0.8 (35)	105 ± 1.2 (19)	104 ± 1.0 (14)	104 ± 1.2 (11)
Litters per pair	4.9 ± 0.0†	4.8 ± 0.2	4.5 ± 0.2*	3.8 ± 0.3*
Live pups per litter	11.8 ±0.3†	1.8 ± 0.3	7.5 ± 0.9*	5.3 ± 0.8*
Percent of live pups	98 ± 1†	99 ± 1	76 ± 6*	71 ± 8*
Live pup weight (g)	1.58 ± 0.02†	1.55 ± 0.02	1.30 ± 0.02*	1.27 ±0.02*
Adjusted live pup weight	1.59 ± 0.02†	1.55 ± 0.02	1.30 ± 0.02*	1.26 ± 0.03*

Data presented as number, percentage, or mean ± SEM; † 5 P < 0.05, test for linear trend;
* 5 P < 0.05, pairwise comparison to controls.
Data for sex ratio and percent pregnant are not shown (cited in Fail et al., 1998).
[a]Number of females delivering a litter/number cohabited with males.
[b]Number of days from initial cohabitation until litter was observed; parentheses enclose number of females.

At necropsy body weight was significantly depressed in the females at 7000 ppm. At all dose levels in the F0 generation liver weights were increased. Of the reproductive organs examined, cauda epididymidalweight was significantly increased at all doses of DMF (Table B45). Further evaluation of sperm parameters indicated a slight decrease in testicular spermatid concentration in the DMF-treated groups that was significant at the low and high doses, with a significant trend. However, DMF had no adverse effect on epididymal spermatozoan concentration, motility, or morphology. Microscopic evaluation of the reproductive organs revealed no histopathology due to DMF treatment.

Table B45. F0 generation: selected organ weights in male Swiss mice at necropsy after dimethylformamide for 29 weeks[a].

	Dimethylformamide (ppm in water)			
Parameter	**0**	**1000**	**4000**	**7000**
Number of animals	20	10	10	10
Right cauda epididymis (mg)	15.2 ± 0.63	18.8 ± 1.1*	18.9 ± 0.93*	17.4 ± 0.84*
Right corpus and caput epididymis (mg)	34.1 ± 1.2	35.6 ± 1.3	36.3 ± 1.6	34.3 ± 1.2
Prostate (mg)	32.6 ± 2.1[j]	32.4 ± 3.1	33.0 ± 2.0	26.9 ± 1.0*
Seminal vesicles with coagulating gland (mg)	594.1 ± 28.7	667.2 ± 54.1	624.2 ± 40.2	570.7 ± 30.6
Right testis (mg)	123.1 ± 4.5	120.0 ± 9.2	121.1 ± 5.5	119.3 ± 4.0
Spermatozoa concentration[b]	1085.9 ± 33.8[j]	900.7 ± 121	917.5 ± 121	1026.9 ± 115.1
Spermatozoa motile[c]	49.2 ± 6.7	46.6 ± 6.1	67.7 ± 10.5	56.8 ± 6.0
Spermatozoa percent abnormal[d]	4.9 ± 0.68	5.3 ± 0.48	4.1 ± 0.70	4.6 ± 0.54
Spermatid count[e]	10.2 ± 0.46j	7.8 ± 0.85*	9.7 ± 0.28	8.3 ± 0.48*

[a]Numbers are mean ± SEM. Each dose group is compared with the control group by Shirley's test if P < 0.10 from Jonckheere's trend test
† P < 0.01), otherwise Dunn's test is applied (* P < 0.05).
[b]Sperm per mg caudal tissue (x 1000).
[c]Samples with at least 100 epididymal sperm.
[d]Dose group means and standard errors are computed only from samples with at least 500 epididymal sperm.
[e]Spermatids per mg testis (x 10,000).

Monitoring of the estrous cycle in control and high dose females revealed a decreased number of females in the high dose group having normal cycles. F1 pup postnatal survival was reduced during pre- and post weaning and body weights of F1 pups in the mid and high dose were also reduced, moreover the surviving pups of these dose groups exhibited craniofacial and sternebral malformations (see section Prenatal Developmental toxicity).

Data generated by a crossover mating trial in the course of the continuous breeding study suggested that the female was the sex affected by DMF treatment because females treated with 7000 ppm DMF produced smaller litters compared to control pairs or the group of control females mated to treated males (Table B46). In addition, pups born by treated females mated to controls exhibited malformations similar to those observed in the F1 pups of the F0 parental generation. The selected animals for the F1 parental generation showed reduced body weights in the mid and high dose groups. DMF was a reproductive toxicant in F1 mice. Affected reproductive performance was seen at the high dose by reduced mating index and at the high and mid dose by reduced pregnancy index and reduced litter size (Table B47)

Table B46. Mating, fertility, and reproductive performance of F0 pairs after a crossover mating trial to determine the affected sex.

Parameter	Dimethylformamide (in drinking water)		
	Control male x control female	7000 ppm male x control female	Control male x 7000 ppm female
Percent fertility[a]	50 (8/16)	69 (11/16)	55 (11/20)
Live pups per litter[c]	8.1 ± 1.9 (8)	10.2 ± 1.2 (11)	5.5 ± 1.0 (11)
Live pup weight (g)[e]	1.56 ± 0.18 (6)	1.63 ± 0.06 (11)	1.44 ± 0.06 (10)
Proportion of pups born alive[e]	0.73 ± 0.16 (8)	0.94 ± 0.04 (11)	0.68 ± 0.12 (11)
Adjusted live pup weight (g)[f]	1.61 ± 0.10	1.66 ± 0.08	1.38 ± 0.08 [b,g]
Average dam weight (g)	40.30 ± 2.06	41.42 ± 1.18	40.74 ± 1.25
Average days to litter	21.6 ± 0.4	22.0 ± 0.7	21.6 ± 0.3

[a]Number of deliveries/number cohabited; * P < 0.05, pairwise comparison to controls.
[b]Treated groups differ from each other at P < 0.05.
[c]Numbers in parentheses are number of dams delivering litters.
[d]Treated groups differ at P < 0.075; ANOVA is P < 0.07.
[e]Numbers in parentheses are number of litters with live pups.
[f]Body weight adjusted statistically (lease square estimate) to account for differences in litter size.
[g]Differs from control at P < 0.09.

Table B47. Mating, fertility, and reproductive performance of second generation breeding pairs[a].

Parameter	Dimethylformamide (ppm in water)			
	0	1000	4000	7000
Percent fertile[b]	90 (18/20) †	90 (18/20)	56(10/18)*	53 (8/15)*
Live F2 pups per litter[c]	11.3 ± 0.7† (18)	11.8 ± 0.4(18)	4.9 ± 1.3* (10)	4.1 ± 1.3* (8)
Proportion of F2 pups born alive	1.00 ± 0.00†	0.99 ± 0.01	0.74 ± 0.14*	0.56 ± 0.15*
Live F2 pup weight (g)	1.59 ± 0.03†	1.48 ± 0.02*	1.30 ± 0.04*	1.32 ± 0.04*
Adjusted live F2 pup weight (g)	1.61 ± 0.02†	1.52 ± 0.02*	1.21 ± 0.04*	1.23 ± 0.04*
Average dam	34.9 ± 0.70†	34.7 ± 0.61	30.2 ± 0.55*	28.9 ± 0.94*

Parameter	Dimethylformamide (ppm in water)			
	0	1000	4000	7000
weight (g)				
Average days to litter	21.2 ± 0.3†	21.6 ± 0.4	23.0 ± 0.7*	23.5 ± 0.7*

[a]Statistical significance for comparisons of dosed groups to controls (* P < 0.05) and significant trends over all groups († P < 0.05).
[b]Percent (number of deliveries/number cohabited).
[c]Numbers in parentheses are number of dams delivering live litters.

The F1 animals of all DMF treated groups had increased liver weights associated with hepatocellular hypertrophy. F1 estrous cycle length was significantly longer in the high dose females compared to the control animals. Histopathology did not reveal any findings in the reproductive tissues of the females. Male animals showed decreased relative prostate weight at all doses and epididymal spermatozoa concentration was reduced at the high dose. (Table B48). No other significant effects of treatment were noted for andrologic parameters. Microscopic
examination of the reproductive organs revealed no other pathology.

Table B48. F1 generation: body and relative organ weights in male swiss mice at necropsy after dimethylformamide[a].

Parameter	Dimethylformamide (ppm in water)			
	0	1000	4000	7000
Number of animals	20	10	10	10
Body (g)	35.4 ± 0.82	37.1 ± 0.76	31.9 ± 0.71*	33.2 ± 0.61*
Liver	58.2 ±0.96	79.7 ± 1.2*	89.5 ± 2.6*	91.1 ± 2.0*
Kidneys/adrenals	20.5 ±0.56	21.3 ± 0.41	21.3 ± 0.49	20.9 ± 0.60
Right cauda epididymis	0.43 ±0.02	0.44 ± 0.01	0.42 ± 0.02	0.46 ± 0.03
Right corpus and caput epididymis	0.92 ±0.02	0.93 ± 0.03	0.98 ± 0.03	0.96 ± 0.02
Prostate	0.71 ±0.03	0.62 ± 0.05*	0.60 ± 0.02*	0.54 ± 0.04*
Seminal vesicles with coagulating gland	11.3±0.33	11.6 ± 0.52	10.8 ± 0.73	10.6 ± 0.88
Right testis	3.6 ±0.11	3.4 ± 0.10	4.0 ± 0.15	3.8 ± 0.14
Spermatozoa concentration[b]	1099.3 ±43.1	1010.3 ± 70.4	979.5 ± 76.7	880.3 ± 58.4*
Spermatozoa (percent motile)[c]	54.9 ±4.1	60.2 ± 4.5	53.4 ± 6.7	65.4 ± 6.0
Spermatozoa percent abnormal[d]	7.4 ±0.65	6.3 ± 0.87	6.1 ± 0.79	7.0 ± 0.34
Spermatid count[e]	9.1 ±0.25	8.4 ± 0.40	9.9 ± 0.40	9.1 ± 0.30

[a]Numbers are mean 6 SEM. Each dose group was compared with the control group by Shirley's test if P < 0.10 from Jonckheere's trend test († P < 0.01), otherwise Dunn's test was applied (* P < 0.05).
[b]Sperm per mg caudal tissue (x 1000).
[c]Samples with at least 100 epididymal sperm.
[d]Dose group means and standard errors are computed only from samples with at least 500 epididymal sperm.
[e]Spermatids per mg testis (x 10,000).

Live F2 pup body weights were reduced at all doses and malformations observed in F2 pups of all DMF treated groups were similar to those observed for F1 litters. Craniofacial and sternebral malformations at the mid and high doses were characteristic and occurred in offspring of both generations (see section Prenatal Developmental toxicity). NOAEL of 1000 ppm (219 mg/kg bw) was established for systemic toxicity of F0 and F1 parental generations as well as their fertility.

Overall on toxicity to reproduction – fertility

There is only one reliable reproductive toxicity study available for DMF in which fertility effects have been addressed. An overview of the effects is presented in Table B49., followed by a conclusion on reproductive toxicity. In the next section prenatal developmental toxicity studies are described.

Table B49. Key study on toxicity for reproduction.

Species, strain, number, sex/group, guideline	Study type, concentration	NOAEL, findings, remarks	Relia-bility*	Reference
Oral				
mouse (CD-1) male/female equivalent or similar to OECD Guideline 416 (two-generation toxicity study)	Multigeneration study (drinking water) 1000, 4000, 7000 ppm (ca. 219, 820 and 1455 mg/kg/d) (nominal in water) Exposure: Continuous breeding protocol (NTP): a dose range-finding phase (optional), an F0 cohabitation and lactation phase, a crossover mating trial of the F0 generation (conducted if F0 reproductive performance is affected), and finally fertility assessment of the F1 generation (born and reared during the F0 lactation phase).	LOAEL (systemic) (P) < 1000 ppm (female) (based on significantly female but not male body weight reduction) NOAEL (reproductive / maternal) (P) < 1000 ppm (male/female) (based on reduced fertility and fecundity at doses above 1000 ppm) LOAEL (reproductive) (F1): 1000 ppm (based on reduced body weight of pups.) NOAEL (teratogenicity) (F1): < 1000 ppm (based on external malformations or other abnormalities, including domed heads and hematomas along the nose and on the head) NOAEL (F2): not determinable (based on malformations of 27.7 % already at the lowest dose, compared to control of 0 % malformations.)	2	Fail, P.A., George, J.D., Grizzle, T.B., and Heindel, J.J. (1998)

Conclusion on fertility and reproductive behavior

Significant reproductive toxicity (e.g. reduced fertility and fecundity characterized by reduced pregnancy and mating index (the latter one only in the high dose group), reduced no. of litters, reduced average litter size and for the F1 parental males by effects on prostate weight and epididymal spermatozoa concentration, the latter finding only in the high dose group) occurred at ≥ 4000 ppm (mean exposure of 820 mg/kg bw/day) in the presence of some general toxicity (i.e. increased liver weights, hepatocellular hypertrophy and decreased body weights in the females at 7000 ppm). Developmental toxicity (e.g. reduced survival and growth of pups, increase in craniofacial and sternebral malformations) was observed in both generations. Reduced F2 pup weight was observed at ≥

1000 ppm (appr. 219 mg/kg bw/day) and reduced F1 pup weight at 4000 ppm. At ≥ 4000 ppm an increase in cranio-facial and sternebral malformations was observed in offspring of both generations.

Prenatal developmental toxicity

Oral

Fail et al., 1998

In a continuous breeding study CD-1 mice were treated orally with DMF in the drinking water at doses of 1000, 4000 and 7000 ppm (about 219, 820 and 1455 mg/kg bw/day) (Fail et al., 1998). Growth and survival of F1 pups were retarded after DMF exposure. The proportion of F1 pups born alive in the final litter and postnatal survival on PND 4 were reduced at the mid- and high-dose levels of DMF (Table B50) and continued to decline throughout the lactation period. Embryo-/fetotoxicity were manifested in reduced body weights of F1 pups in the mid and high dose (Table B48). Moreover, the surviving pups of these dose groups exhibited craniofacial and sternebral malformations. The F1 animals of all DMF treated groups had increased liver weights associated with hepatocellular hypertrophy. Histopathology did not reveal any findings in the reproductive tissues of the females. Live F2 pup body weights were reduced at all doses and malformations observed in F2 pups of all DMF treated groups were similar to those observed for F1 litters. Craniofacial and sternebral malformations at the mid and high doses were characteristic and occurred in offspring of both generations. The more severe malformations were incompatible with life. Those animals less affected did grow to maturity, although examination after necropsy indicated the malformations present at birth had persisted through young adulthood. Developmental effects observed in this study were at dose levels associated with maternal toxicity, which was displayed in reduced body weight, reduced fertility, affected estrous cycle, reduced mating indices and increased mortality of pups. NOAEL of 1000 ppm (219 mg/kg bw) was established for developmental toxicity for both generations.

Table B50. Average postnatal survival of final litter from continuous breeding phase[a].

	Dimethylformamide (ppm in water)			
Postnatal age (days)	**0**	**1000**	**4000**	**7000**
0	0.96 ± 0.03† (37)	0.94 ± 0.05 (19)	0.67 ± 0.09* (19)	0.59 ± 0.12* (15)
4	0.92 ± 0.04† (36)	1.00 ± 0.00 (18)	0.51 ± 0.10* (16)	0.43 ± 0.14* (10)
7	0.85 ± 0.05† (36)	0.95 ± 0.03 (18)	0.50 ± 0.10* (16)	0.41 ± 0.14* (10)
14	0.76 ± 0.06† (36)	0.82 ± 0.04 (18)	0.32 ± 0.09* (16)	0.38 ± 0.14* (10)
21	0.66 ± 0.07† (36)	0.79 ± 0.05 (18)	0.29 ± 0.09* (16)	0.36 ± 0.14* (10)

[a]Numbers are mean ± SEM (mean number of live pups/number born alive). Increases in survival over time were due to initial missexing of pups (number of litters in parentheses). Each dose group was compared to the control with Shirley's test when a trend was present ($P < 0.10$ from Jonckheere's trend test, otherwise, Dunn's test was applied (* $P < 0.05$; † 5 $P < 0.01$ on trend test).

Hellwig et al., 1991

In a supporting developmental toxicity study with Sprague-Dawley rats and NMRI mice, treated with DMF at dose levels of 166, 503 and 1510 mg/kg bw and 182 and 548 mg/kg bw, respectively, an increased number of malformations was observed in the absence of overt maternal toxicity (Table B51). In rats, 63 % of the implantations were resorbed in the highest dose group. Among the surviving foetuses, 11.76 % had skeletal anomalies. In the mid-dose group (503 mg/kg bw), an increase in early and late resorptions was observed. Foetal body weight was reduced and the number of malformation, variations and skeletal retardation was increased. At 166 mg/kg body weight/day a slight increase in early resorptions and a decrease in placental weights were recorded. In mice, 548 and 182 mg/kg body weight/day led to a decrease in foetal weights and an increase in the number of retardations and variations (Table B51). The LOAEL was 182 mg/kg bw /day in mice and NOAEL of 166 mg/kg bw /day in rats for maternal toxicity, embryo-/foetotoxicity and teratogenicity.

Table B51. Effects of oral administration (gavage) of DMF to pregnant rats and mice.

	Rats (dose, mg/kg bw)						Mice (mg/kg bw)			
	Con-trol	166	Con-trol	503	Con-trol	1510	Con-trol	182	Con-trol	548
No. of animals	20	20	25	26	24	22	26	26	26	26
No. of pregnant animals	18	19	22	23	23	20	23	24	23	24
Dead animals	0	0	0	0	0	1	0	0	0	0
No. of animals with abortions	0	0	0	0	0	0	1	1	0	0
—no. of aborted foetuses							12	13	—	—
Implantations total	230	252	296	296	291	232	255	301	283	281
Implantations per animal	12.78	13.26	13.45	12.87	12.65	11.60	12.09	12.54	12.3	11.71
Live foetuses total	223	235	279	264	265	85	210	245	229	241
Live foetuses per dam	12.39	12.37	12.68	11.48	11.52	4.25	9.13	10.21	9.96	10.04
Dead foetuses	0	0	0	0	0	0	1	1	2	2
Early resorptions (including Salewski)	6	15	16	21	25	22	19	25	35	29
Medium-term resorptions	0	1	1	1	1	116	3	4	6	4
Late resorptions	1	1	0	10	0	9	10	13	11	5
Total resorptions	7	17	17	32*	26	147**	33	43	54	40
—% per implantations	3.04	6.75	5.74	10.81	8.93	63.36	12.94	14.29	19.08	14.23
Foetal weight, mean	3.71	3.79 ††	3.84	3.23 ††	3.87	2.73 ††	1.11	1.05	1.17	1.03 *
Foetal length, mean	3.60	3.63 †	3.64	3.47 ††	3.65	3.15 ††	2.25	2.20 ††	2.28	2.22 **
Placental weight, mean	0.52	0.50 ††	0.57	0.44 ††	0.53	0.34 ††	0.08	0.08	0.08	0.08
Runts total	1	2	1	28	0	55.0	6	18	3	16
Anomalies	0	0	2	25**	13	10.0 *	1	4	2	17**
—% live foetuses	0	0	0.72	9.47	4.91	11.76	0.48	1.63	0.87	7.05

* Significant at 95 % (chi-square test).
** Significant at 99 % (chi-square test).
† Significant at 95 % (t-test).
†† Significant at 99 % (t-test).

Saillenfait et al., 1997

In another supporting developmental toxicity study with Sprague-Dawley rats, the animals received 50, 100, 200 and 300 mg DMF/kg bw/day by gavage from gestation day 6 – 20. Maternal toxicity was observed at doses from 100 up to 300 mg/kg bw/day characterized by dose dependent impairment of body weight gain and food consumption. Fetotoxicity occurred also at these dose levels (e.g. dose-related decrease in fetal body weight/litter (Table B52), dose-dependent increase in the total number with skeletal variations, statistically significant at 200 and 300 mg/kg bw/day (Table B53)). The total number of skeletal variations was also slightly (but not statistically significant) increased at 50 mg/kg bw/day, thus suggesting slight indications for fetotoxicity at this dose level. Teratogenicity was

not observed. NOAEL for maternal toxicity and LOAEL for embryo-/fetotoxicity was 50 mg/kg bw, while NOAEL for teratogenicity was 300 mg/kg bw.

Table B52. Reproductive Parameters in Sprague–Dawley Rats Treated Daily by Gastric Intubation with N,N-Dimethylformamide on Days 6 to 20 of Gestation.

Findings	Dose (mg/kg bw)				
	0	50	100	200	300
No. of deaths per No. of treated females	0/24	0/22	0/22	0/22	0/22
Percentage of females pregnant	66.7	95.5*	86.4	86.4	90.9
No. of litters examined	16	21	19	19	20
Mean implantation sites per litter	15.81 ± 0.43[a]	14.48 ± 0.96	15.47 ± 0.70	15.53 ± 0.63	15.25 ± 0.61
Mean live fetuses per litter	15.25 ± 0.49	13.81 ± 0.94	14.79 ± 0.71	14.58 ± 0.64	14.05 ± 0.62
Mean percentage of resorption sites per litter	3.71 ± 1.25	8.62 ± 4.71	4.45 ± 0.98	6.15 ± 1.08	7.55 ± 2.05
Fetal sex ratio M/F	1.05	0.91	0.90	1.08	0.92
Mean fetal body weight per litter (g)					
All fetuses	5.54 ± 0.05	5.52 ± 0.04	5.30 ± 0.05**	4.87 ± 0.05**	4.76 ± 0.06**
Male fetuses	5.65 ± 0.07	5.66 ± 0.05	5.43 ± 0.06	4.99 ± 0.08**	4.90 ± 0.09**
Female fetuses	5.43 ± 0.07	5.38 ± 0.05	5.16 ± 0.07*	4.75 ± 0.07**	4.62 ± 0.09**

[a] Values are expressed as means ± SEM.
*,** Significant differences from the vehicle control value, $p < 0.05$ and $p < 0.01$, respectively.

Table B53. Incidence of Malformations and Variations in Fetuses of Sprague–Dawley Rats Treated Daily by Gastric Intubation with N,N-Dimethylformamide on Days 6 to 20 of Gestation.

Findings	Dose (mg/kg bw)				
	0	50	100	200	300
	Number of foetuses (litters) examined				
External examination	244 (16)	290 (20)	281 (19)	277 (19)	281 (20)
Visceral examination	122 (16)	145 (20)	141 (19)	138 (19)	141 (20)
Skeletal examination	122 (16)	145 (20)	140 (19)	139 (19)	140 (20)
Malformations [a]	Number of foetuses (litters) affected				
Exophtalmia bilateral	0	0	0	0	1 (1)
Encephalocele	0	0	0	0	1 (1)
Agnatia	0	0	0	0	1 (1)
Absence of nasal septum	0	0	0	0	1 (1)
Interventricular septum defect	0	1 (1)	0	0	0
Diaphragmatic hernia	0	1 (1)	1 (1)	0	0
Hydronephrosis (bilateral)	0	0	0	1(1)	1 (1)
Total number with malformations	0	2 (2)	1 (1)	1 (1)	2 (2)
External variations					
Hindlimb talipes	0	0	0	1(1)	0
Rudimentary tail	0	0	1 (1)	0	0
Total number with external variations	0	0	1 (1)	1 (1)	0

Findings	Dose (mg/kg bw)				
	0	**50**	**100**	**200**	**300**
Visceral variations					
Dilated renal pelvis	4 (2)	5 (5)	0	1 (1)	1 (1)
Dilated ureter	17(8)	6 (4)	5 (5)	4 (4)	10 (4)
Total number with visceral variations	17(8)	10 (8)	5 (5)	5 (5)	11 (5)
Skeletal variations					
Skull					
Parietals, incomplete ossification	2 (1)	0	0	0	0
Supraoccipital					
Incomplete ossification (moderate)	0	1 (1)	8 (6)	52 (16)**	49 (17)**
Absent or incomplete ossification					
(severe)	0	1 (1)	1 (1)	12 (9)*	70 (16)**
Total	0	2 (2)	9 (7)	64 (16)**	119 (20)**
Total number with skull variations	2(1)	2 (2)	9 (7)	64 (16)**	119 (20)**
Sternebrae					
Fifth absent or incomplete ossification	3 (2)	12(6)	13 (7)	15 (11)*	32 (13)**
Second and fifth absent	0	1 (1)	0	0	0
Total	3 (2)	13 (7)	13 (7)	15 (11)*	32 (13)**
Ribs					
13th short	0000				(1)
Extra cervical	2 (2)	2 (2)	1 (1)	1 (1)	1 (1)
Extralumbar	11 (7)	8 (4)	7 (7)	4 (3)	1 (1)
Vertebral centra, incomplete ossification	8 (7)	11 (7)	26 (11)	19 (10)	8 (4)
Total number with skeletal variations	21 (11)	34 (13)	48 (16)	81 (19)**	125 (20)**

[a] One fetus in the 300 mg DMF/kg group had ablepharia, exophtalmia, encephalocele, agnatia, and absence of nasal septum.
*,** Significant differences from the vehicle control value, $p < 0.05$ and $p < 0.01$, respectively.

BASF, 1976d; Merkle and Zeller, 1980

In an oral developmental study with Hymalayan rabbits, ca. 44.1, 65, and 190 mg/kg bw/day were administered per gavage to the animals during the gestation period (day 6-18 post insemination). All animals survived until termination of the study. In the high dose group, maternal toxicity was observed. Body weight was significantly reduced at the end of the treatment period and also on day 28 p.i., body weight gain was significantly reduced (animals even lost weight) during the entire treatment period that was also true for food consumption. 3 dams aborted, one on day 21, one on day 24 and one on day 28 p.i.. At necropsy the liver of 1 dam was of a clay-like color. Fertility index, number of *corpora lutea*, number of implantations and the ratio of live/dead fetuses were unaffected. n the mid dose group, no clinical signs of toxicity were observed. Transiently reduced food consumption was noted during the treatment period, however, this had no effect on body weight or body weight gain. Gross necropsy revealed a clay-like colored liver in 1 dam. Mean number of implantation and percentage of live fetuses was decreased; however a dose-response relationship was missing for this finding. In the low dose group, no deaths or clinical signs of toxicity were noted except a transient reduction of food consumption during the treatment period without any effect on body weight or body weight gain. No substance related pathological findings were recorded, gestational and fetal parameters were

unaffected.
Among embryotoxic including teratogenic effects, placental weights and fetal weights as well as fetal length were significantly decreased in the highest dose group. The incidence of malformed fetuses observed in 7 litters was increased (16/45 = 35.5 %); hydrocephalus internus (6 fetuses), exophthalmia (2 fetuses), ectopia visceralis (3 fetuses), hernia umbilicalis (7 fetuses) and cleft palate (1 fetus) were observed. Three fetuses showed multiple malformations. In the mid dose group, fetal parameters, number and type of variations and retardations were unchanged. Three malformed fetuses in two litters were found. This incidence was not statistically different from control, however, the type of malformation (hydrocephalus internus) indicated a substance-related effect. In the low dose group, one fetus with malformation (hydrocephalus internus) was found, however, this incidence was in the range of control. NOAEl of 65 and 44.1 mg/kg bw was established for embryo-/fetotoxicity and maternal toxicity and teratogenicity, respectively.

Inhalation

BASF AG , 1989b; Hellwig et al., 1991

In an inhalation developmental toxicity study rats and Hymalayan rabbits were exposed to DMF vapour by whole-body exposure. Rats were exposed to 0 (control) or 287 ppm at different time during the gestation period. Rabbits were exposed to 50, 150 or 450 ppm ((about 150, 450 and 1360 mg/m^3) on day 7 through day 19 post insemination (p.i.) for 6 hours/day.
In rats, the exposure led to a reduced maternal weight gain from the beginning of treatment. An increase in early resorptions and dead implantations was observed. Foetal weights were decreased and the number of variations and retardations was increased. In rabbits, maternal toxicity was observed at the mid and the highest concentration and clear signs of embryo-/fetotoxicity including indications of teratogenicity were seen at the highest concentration tested. Embryo-/fetotoxicity resulted in significantly reduced fetal body weights (i.e. mean fetal body weight was 37.7 g in comparison to 43.7 g in the concurrent control group; Table B54). In this group, the incidence of malformations (especially hernia umbilicalis in 7 out of 86 fetuses in 4 out of 15 litters) and variations (mainly skeletal, i.e. skull bones and sternebrae) was significantly increased. A slight increase was found for external variations (i.e. pseudoankylosis in 6 out of 86 fetuses in 2 of 15 litters). Total malformations occurred at a fetal incidence of 15 and a litter incidence of 9 at 1.36 mg/L in comparison to a fetal incidence of 3 and a litter incidence of 2 in the concurrent control. Fetal and litter incidences for total variations at 1360 mg/m³ were 77 and 15, respectively in comparison to 29 and 11 in the concurrent control. One hernia umbilicalis among 75 fetuses was observed in the 450 mg/m³ group, the number of skeletal variations was also increased in this group but without being statistical significant. Only marginal maternal effects (impaired body weight) were observed at the mid concentration of 450 mg/m³. NOAEC of 150 mg/m³ (50 ppm) was established for rabbits for maternal as well as for embryo-/fetotoxicity including teratogenicity.

Table B54. Effects of inhalation exposure to DMF in pregnant rabbits.

	Dose			
	Group 0 (control)	**Group 1 (50 ppm)**	**Group 2 (150 ppm)**	**Group 3 (450 ppm)**
No. of animals	15	15	15	15
No. of litters (obtained and investigated)	12	14	14	15
Mean maternal body-weight change during gestation (g)				
—days 7-19	31.0	42.4	3.1	-34.3
—days 0-29	248.1	202.1	146.4	183.0
Dead foetuses	0	0	3	0
Corpora lutea	8.3*	8.2	8.2	8.6
Implantation sites	6.3*	5.9	6.7	6.4
Preimplantation loss (%)	22.8†	29.3	16.9	24.3

	Dose			
	Group 0 (control)	**Group 1 (50 ppm)**	**Group 2 (150 ppm)**	**Group 3 (450 ppm)**
Post implantation loss (%)	9.5†	11.3	22.6	14.5
Resorptions total	8	12	19	10
Live foetuses (obtained and investigated)	67	71	72	86
Foetal weights (g)	43.7*	42.1	41.7	37.7[b]
External malformations (foetal incidence)	0	1	1	8 [b]
—litter incidence	0	1	1	5 [a]
Hernia umbilicalis	0	0	1	7 [a]
—litter incidence	0	0	1	4
—foetuses with multiple malformations	0	1	0	1
External variations	0	1	3	6 [a]
—litter incidence	0	1	2	2
Pseudoankylosis (forelimb)	0	0	3	6 [a]
—litter incidence	0	0	2	2
Soft tissue malformations	2	2	3	7
—litter incidence	2	2	3	5
—agenesia of spleen and/or gall bladder	0	0	0	3
—septal defect	2	1	3	3
Soft tissue variations	21	17	21	30
—litter incidence	11	10	10	14
Skeletal malformations	1	1	0	4
—litter incidence	1	1	0	4
Skeletal variations	10	8	16	73[b]
—litter incidence	6	7	10	15[b]
Skeletal retardations	33	30	29	23 [b]
—litter incidence	11	10	14	10
Fused sternebrae	5	2	13	51 [b]
Irregular sternebrae	2	3	1	34[b]
Bipartite sternebrae	0	0	0	12 [b]
Accessory 13th rib	1	2	2	7
Total malformations (foetal incidence)	3	2	4	15 [a]
—litter incidence	2	2	4	9 [a]
Total variations (foetal incidence)	29	23	32	77 [b]
—litter incidence	11	12	12	15

*Means.
†Mean %.
[a] $p < 0.05$. [b] $p < 0.01$.

In two inhalation supporting studies Long-Evans rats (Kimmerle and Machemer, 1975) and Sprague-Dawley rats (TSCATS: OTS 0516779, 1978) were exposed from day 6 to day 15 of gestation, 6 hours/day to exposure levels of 18 and 172 ppm (about 55 and 520 mg/m³) and to 30 and 300 ppm (about 90 and 910 mg/m³), respectively. In both studies teratogenicity was not observed, however fetotoxicity occurred at 172 ppm in the Long-Evans fetuses without signs of maternal toxicity whereas maternal toxicity and fetotoxicity were observed in the Sprague-Dawley rats at the exposure level of 300 ppm. In the Long-Evans fetuses fetotoxicity was represented by significantly reduced body weights in comparison to the control fetuses and in the Sprague-Dawley fetuses by significantly reduced fetal weights and a significant higher incidence of fetuses with ossification variations in comparison to the control fetuses. NOAEC of 172 ppm and 18 ppm for maternal toxicity/ teratogenicity and foetotoxicity were established for Long Evans rats, respectively. NOAEC of 30 and 300 ppm were established for maternal toxicity/ foetotoxicity and teratogenicity for Sprague Dawley rats, respectively.

Dermal

Hellwig et al., 1991; BASF, 1984

In a dermal developmental toxicity study (OECD Guideline 414, (1981)) with rats doses of 94, 472 and 944 mg/kg bw were administered in an open epicutaneous system for 3 hour /day on clipped dorsal area from days 6 to 10 and 15 to 15 of gestation. Rabbits were administered dermally to 100, 200 and 400 mg/kg bw/day for 6 hours/day on shaved dorsal skin from day 6 to 18 post insemination. In rats, dose dependent incidence of teratogenicity was observed in the absence of overt maternal toxicity. 2.46 %, 3.05 % and 5.46 % of live foetuses showed anomalies in treated groups of 94, 472 and 944 mg/kg bw, respectively (Table B55). No NOAEL could be established.

Table B55. Effects of dermal administration of DMF to pregnant rats†.

Rats	Group 1 (control)	Group 2 (94 mg/kg)	Group 3 (472 mg/kg)	Group 4 (944 mg/kg)
No. of pregnant animals				
(and litters investigated)	10(10)	22(22)	21(20)	22(22)
Body-weight gain (g) day 0-5 (means)	55.5	62.64	53.52	45.68*
Dead animals	0	0	0	0
Animals with abortions	0	0	0	0
Total number of implantations	108	279	260	275
Implantations per dam (means)	10.80	12.68*	12.38	12.50
Live foetuses	105	268	253	258
Total resorptions	3	11	7	17
Early (Salewski) resorptions	0	0	0	0
Early resorptions	3	9	4	12
Medium-term resorptions	0	2	3	5
Late resorptions	0	0	0	0
Foetal weight, means	3.60	3.67	3.77	3.61
Foetal length, means	3.63	3.60	3.61	3.52**
Placental weight, means	0.69	0.59**	0.56**	0.58**
Runts, total	0	1	2	1
Number of malformed foetuses	0	7	7	14
—litter incidence (and % of litters)	0	6(27.27)	5(25)	9(40.1)
—% of live foetuses with malformations per litter	0	2.46	3.05	5.46*
—split thoracic vertebrae ‡	0	3	2	2
—fused ribs	0	1	0	0
—wavy ribs, bilateral	0	0	2	9
—wavy ribs, unilateral	0	2	3	3
Variations and retardations (foetuses)	14	38	42	58
—litter incidence (and % of litters)	7(70)	15(68.2)	18(90)	19 (86.4)
—% of live foetuses per litter	13.86	13.16	16.90	22.08
Foetuses with partial sternal ossification	6	22	18	32
Sternal aplasia	2	8	10	10
Sternal displacement ‡	2	3	4	8

*Significant at 95 %.
**Significant at 99 %.
† Exposure periods day 6-10 and 13-15 of gestation.
‡ No details on symmetry were recorded.

In rabbits, at the high dose signs of maternal toxicity and embryo-/fetotoxicity were observed. One dead fetus and several malformations (e. g. hernia umbilicalis, skeletal malformations) were found at this dose level (Table B56). No embryo-/fetotoxic effects were found at the low and mid dose. The 3 fetuses with malformations seen in the low dose were regarded to be incidental, since no malformations

occurred in the fetuses at the mid-dose. Thus, according to the authors, disregarding the skin reactions, the NOAEL for maternal toxicity as well as for embryo-/fetotoxicity and teratogenicity was 200 mg/kg bw/day.

Table B56. Effects of dermal administration of DMF to pregnant rabbits.

Rabbits	Group 1 (control)	Group 2 (100 mg/kg)	Group 3 (200 mg/kg)	Group 4 (400 mg/kg)
No. of animals	13	15	14	14
No. of litters investigated	13	15	14	14
Corpora lutea				
—total	105	118	106	106
—per doe	8.08†	7.87	7.57	7.57
Implantations				
—total	85	92	83	87
—per doe	6.54†	6.13	5.93	6.21
Live foetuses				
—total	75	80	73	75
—per doe	5.77†	5.33	5.21	5.36
Dead implantations				
—total	10	12	10	12
—per doe	0.77†	0.80	0.71	0.86
% Implantation/animal	12.39†	11.66	11.35	13.08
Maternal body weights (g) on day 18 post insemination	2607.50	2571.20	2501.21	2461.60*
Resorptions early (Salewski)	0	0	0	0
Resorptions early	1	7	2	6
Resorptions intermediate	6	4	7	5
Resorptions late	3	1	1	0
Dead foetuses	0	0	0	1
Foetuses investigated	75	80	73	75
Foetal weight	43.41†	41.81	43.10	40.94
Anomalies				
—Litters	0	2	0	9
% litters	0.0	13.33f	0.0	64.29**
—Foetuses	0	3	0	21
% foetuses/litter	0.0	3.33f	0.0	31.00**
Variations				
—Litters	10	13	12	13
% litters	76.92	86.67	85.71	92.86
—Foetuses	36	40	47	39
% foetuses/litter	42.38f	49.01	62.89	53.23
Retardations				
—Litters	13	15	13	13
% litters	100.00	100.00	92.86	92.86
—Foetuses	55	54	35	34
% foetuses/litter	73.16†	65.29	49.93	43.76

*Significant at 95 %.
**Significant at 99 % in relation to Group 1
†Means.

Overall on developmental toxicity studies

An overview of key studies on developmental toxicity is provided in Table B57, followed by conclusions on developmental toxicity per route of administration.

Table B57. Key developmental toxicity studies of DMF (adopted from registration dossier and OECD SIDS, 2004).

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Reliability*	Reference
Oral				
Mice (CD-1), 20 pregnant females/ dose group Oral: drinking water	1000, 4000, 7000 ppm (ca. 219, 820 and 1455 mg/kg/d) (nominal in water) Vehicle: deionized/filtered drinking water Duration: continuous breeding protocol up to 21 day of lactation phase of F1 animals	NOAEL for fertility (F0, F1) and developmental toxicity (F1): 219 mg/kg bw; LOAEL for parental generation and systemic toxicity (F0, F1), and developmental toxicity of F2: 219 mg/kg bw 7000 ppm (1455 mg/kg bw) and 4000 ppm (820 mg/kg bw): Dams F0: liver weights ↑, fertility ↓, BW ↓, FC ↓, Litter size↓, estous cycle ↑ Foetuses F1: liver weights ↑, malformations ↑ (external, craniofacial and sternebral), BW ↓, estrous cycle length ↑, relative prostate weight↓, spermatozoa concentration ↓, mating index ↓, pregnancy index ↓. Foetuses F2: malformations ↑ (external, craniofacial and sternebral); BW ↓, 1000 ppm (219 mg/kg bw): Dams F0: liver weights ↑ Foetuses F1: liver weights ↑ Foetuses F2: malformations ↑ (external, craniofacial and sternebral); BW ↓	2	Fail, P.A., George, J.D., Grizzle, T.B., and Heindel, J.J. (1998)
Rats (Sprague Dawley), 19 (untreated control), 23 pregnant females/ dose group Oral: gavage	166, 503 and 1510 mg/kg bw; Duration: GD 6 – 15	NOAEL for maternal, embryo-/foetotoxicity and teratogenicity: 166 mg/kg bw 503 and 1510 mg/kg bw: Dams: one animal dead (1510 mg/kg bw), BW ↓, resorptions ↑ Foetuses: BW ↓, skeletal malformations, variations, retardations ↑. 166 mg/kg bw: Dams: no maternal effects, resorptions ↑ (slightly)	2	Hellwig et al., 1991; BASF, 1976d

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia-bility*	Reference
		Foetuses: placental weight ↓ (slightly)		
Mice (NMRI), 23 (untreated control), 24 (treated) of pregnant females/dose Oral: gavage.	182 and 548 mg/kg bw Duration: GD 6 – 15	LOAEL for maternal, embryo-/foetotoxicity and teratogenicity: 182 mg/kg bw 548 mg/kg bw: Dams: no maternal effects; liveborn foetuses ↓ Foetuses: BW↓, retardations and variations ↑, skeletal malformations ↑ 182 mg/kg bw: Dams: no maternal effects; liveborn foetuses ↓ Foetuses: BW ↓, retardations and variations ↑, skeletal malformations ↑ (slightly)	2	
Rats (Sprague Dawley) 22-24 pregnant females /group Oral: gavage	50, 100, 200, 300 mg/kg Duration: GD 6 – 20	NOAEL for maternal toxicity and embryo-/fetotoxicity: 50 mg/kg bw; NOAEL for teratogenicity: 300 mg/kg bw 100, 200, and 300 mg/kg bw: Dams: BWG ↓, FC ↓ Foetuses: BW↓, single occurrence of external and visceral malformations. No specific pattern of malformations; incidence of two skeletal variations ↑ 50 mg/kg bw Dams: no effects Foetuses: no effects; skeletal variations ↑ (no statistically significant)	2	Saillenfait et al., 1997
Rabbit (Hymalayan) Oral: gavage; 24, 12, 18, and 11 females were used for untreated control, low dose, mid dose, and high dose group, respectively.	46.4, 68.1 and 200 µL/kg bw/day (about 44.1, 65 and 190 mg/kg bw/day) Duration: GD 6 – 18	NOAEL for maternal toxicity and embryo-/fetotoxicity: 65 mg/kg bw; NOAEL for teratogenicity: 44.1 mg/kg bw 190 mg/kg bw Dams: BW ↓, BWG ↓, FC ↓, abortion ↑, Foetuses: BW↓, placental weight ↓, malformations ↑ 65 mg/kg bw: Dams: no maternal effects, FC ↓ (slightly) Foetuses: skeletal malformations ↑ (slightly)	2	BASF, 1976 Merkle and Zeller, 1980

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia-bility*	Reference
		44.1 mg/kg bw: Dams: no maternal effects Foetuses: one foetus with malformations (within control data)		
Inhalation				
Rabbit (Hymalayan) Inhalation: vapour (whole body)	50, 150 and 450 ppm (150, 450 and 1360 mg/m³) Duration: GD 7 – 19 for 6 hours/day	NOAEL for maternal toxicity, embryo-/fetotoxicity and teratogenicity: 50 ppm (ca. 150mg/m³) 450 ppm (1360 mg/m³): Dams: BW ↓ (d 7-10), BWG↓, no clinical signs Foetuses: BW↓, malformations (external, skeletal, visceral)↑ 150 ppm (450 mg/m³): Dams: BW static, no clinical signs Foetuses: one foetus with hernia umbilicalis, sternal variations ↑ 50 ppm (150 mg/m³): Dams: BW↑, no clinical signs Foetuses: no effects	1	BASF (1989b) Hellwig et al. (1991)
Rats (Sprague Dawley), 30 pregnant females /dose group Inhalation: vapour (whole body)	0 or 287 ppm Experiment I: exposure on GD 0-1, 4-8, 11-15 and 18-19 for 6 hours/day; Experiment II: exposure on GD 0-3, 6-10, and 11-18 for 6 hours/day.	No NOAEC established: 287 ppm: Dams: BW↓, early resorptions ↑, dead implantations ↑ Foetuses: BW↓, variations ↑, retardations ↑	2	
Rat (Sprague Dawley), 21 pregnant females/ dose group Inhalation	30 or 300 ppm (90 and 910 mg/m³) Duration: GD 6 – 15 for 6 hours/day	NOAEC for maternal toxicity and fetotoxicity: 30 ppm (90 mg/m³); NOAEC for teratogenicity: 300 ppm (910 mg/m³) 300 ppm: Dams: BWG↓ (GD 5-16) Foetuses: BW↓, ossification variations ↑	2	TSCATS: OTS 0516779 (1978)

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Reliability*	Reference
		30 ppm: Dams: no treatment related effects Foetuses: no treatment related effects		
Rats (Long Evans) Inhalation	18 or 172 ppm (about 55 and 520 mg/m³)	NOAEC for maternal toxicity and teratogenicity: 172 ppm (520 mg/m³); NOAEC for fetotoxicity: 18 ppm (55 mg/m³) 172 ppm: Dams: no signs of maternal toxicity Foetuses: BW↓	2	Kimmerle and Machemer (1975)
Dermal				
Rabbits (Hymalayan), 15 does per group Application on shaved area of dorsal skin: semi-occlusive	100, 200 and 400 mg/kg bw/day; Duration: GD 6 – 18 for 6 hours /day	NOAEL for maternal, embryo-/foetotoxicity and teratogenicity: 200 mg/kg bw 400 mg/kg bw: Dams: significant skin irritation, BWG↓ (GD 16-18), preimplantation losses (not significant) Foetuses: BW not affected, skeletal and visceral malformations ↑ 200 mg/kg bw: Dams: no treatment related effects Foetuses: no treatment related effects	1	BASF AG (1984) Hellwig et al. (1991)
Rats (Sprague Dawley), 21-22 pregnant females Application on a clipped dorsal area: open epicutaneous system	94, 472 and 944 mg/kg bw; Duration: GD 6-10, 13-15 for 3 hours /day	No NOAEL could be established 944 mg/kg bw: Dams: BWG↓ (GD 0-15), placental weights↓ Foetuses: BW not affected, foetal lengths ↓, skeletal and visceral malformations ↑, variations and retardations↑ 472 and 94 mg/kg bw: Dams: placental weights↓ Foetuses: foetal lengths ↓ (not significant), variations and retardations↑	2	

Conclusion developmental toxicity

The developmental toxicity of DMF was investigated in 9 studies of which four by oral, three by inhalation routes and one by dermal route. The animal species were rats (Sprague Dawley, Long Evans), mice (CD-1 and NMRI) and Hymalayan rabbits. Generally, embryo-/fetotoxicity were manifested by reduced body weights of pups and reduced number of litters while teratogenicity resulted

in a variety of skeletal malformations.

In the oral exposure studies in Sprague Dawley rats, CD-1 mice and Hymalayan rabbits embryo-/fetotoxicity and teratogenicity was mostly observed at maternal toxic doses while no teratogenicity was observed in the study Sprague Sawley rats. NOAEL of 50 and 166 mg/kg bw were established for maternal effects and embryo-/fetotoxicity in two studies, whereby NOAEL of 300 mg/kg bw, the highest dose level tested was established for teratogenicity in the study with Sprague Dawley rats. The overall NOAEL of 219 mg/kg bw was established for developmental effects for F1 and F2 in the continuous breeding study with CD-1 mice. In contrast, in NMRI mice embryo-/fetotoxicity and/or indications for teratogenicity were found at dose levels without maternal toxicity. In this study, NOAEL of 548 mg/kg bw and 182 mg/kg bw were established for maternal toxicity and for embryo-/fetotoxicity and teratogenicity, respectively. In the study with rabbits, at the highest dose level (190 mg/kg bw) clear signs of embryo-/fetotoxicity and teratogenicity were observed (e.g. decreased placental and fetal weights, increased incidence of malformed fetuses showing mainly hydrocephalus internus, hernia umbilicalis and/or ectopia visceralis). In the mid and low dose group (65 and 44.1 mg/kg bw) teratogenic effects were observed without signs of maternal toxicity. In the mid dose group no maternal toxicity was observed but three malformed fetuses in two litters with hydrocephalus internus indicated a substance-related teratogenic effect. At the low dose one fetus showed hydrocephalus internus, however, this incidence was in the range of control data. Based on the results of these oral developmental studies, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF with NOAEL of 44.1 mg/kg bw for teratogenicity.

In the inhalation developmental studies in rats (Sprague Dawley and Long Evans) and rabbits embryo-/fetotoxicity and teratogenicity was also observed at maternal toxic concentrations. NOAEC of 150 mg/m³, the lowest concentration tested, was established for rabbits for maternal as well as for embryo-/fetotoxicity including teratogenicity. In both strains of rats, no teratogenicity was observed and NOAEC of 520 mg/m³ and 990 mg/m³, the highest concentrations tested, were established. However, foetoxicity at maternal toxic concentration of 90 mg/m³, the lowest level tested, was observed in Sprague Dawley rats. This was the same findings as that in the oral study with the same strain of rats. There was no teratogenicity observed up to the highest dose level while embryo-/fetotoxicity occurred at maternal dose (Saillenfait et al., 1997). In the study with Long Evans rats, fetotoxicity was observed at 55 mg/m³, the lowest concentration tested, at which no signs of maternal toxicity were observed. Based on the results of these inhalation studies, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF with NOAEC of 50 mg/m³.

In the dermal inhalation study in Hymalayan rabbits, only very mild signs of maternal toxicity were observed at the highest dose level (400 mg/kg bw). One dead fetus and several malformations (e.g. hernia umbilicalis, skeletal malformations) were found at this dose level. No embryo-/fetotoxic effects were found at the low and mid dose.
NOAEL of 200 mg/kg bw (mid dose) was established for maternal effects and embryo-/fetotoxicity and teratogenicity.

Since rabbit appeared to be the most sensitive species that the rats or mice, NOAEL of 200 mg/kg bw and NOAEC of 150 mg/m³ established in the dermal and inhalation developmental studies, respectively, were used as POD for the DNEL for systemic effects by dermal route and inhalation routes of exposure.

Overall on toxicity to reproduction – fertility and developmental effects

One continuous breeding study in mice and 9 developmental studies were available as key studies for assessment of reproductive toxicity. In the continuous breeding study in mice, DMF produced reproductive toxic effects. In the studies in rats embryo-/fetotoxicity was mostly seen at maternal toxic doses/concentrations and teratogenicity was observed at maternal toxic doses/concentrations only, whereas in mice and in rabbits embryo-/fetotoxicity and/or indications for teratogenicity were found at dose levels without maternal toxicity. Based on the findings in these studies, rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF. Therefore, PODs for developmental

effects and fertility were determined based on developmental studies in rabbits. (Table B58).

Table B58. Point of departures for reproductive and developmental toxicity.

POD for DNEL derivation (endpoint)	Species and duration	NOAEL (mg/kg bw) /NOAEC ppm (mg/m³)	Toxicological endpoint	Reference
Maternal toxicity				
Inhalation	Rabbit , GD 7 – 19	150 mg/m³	Decreased body weight and body weight gain	BASF (1989b) Hellwig et al. (1991)
Dermal	Rabbit, GD 6 – 18	200 mg/kg bw/day	Decreased body weight gain	BASF AG (1984) Hellwig et al. (1991a)
Prenatal developmental toxicity				
Inhalation	Rabbit , GD 7 – 19	150 mg/m³	Decreased foetal body weight, increased number of malformations (external, skeletal, visceral) and sternal variations	BASF (1989b) Hellwig et al. (1991)
Dermal	Rabbit, GD 6 – 18	200 mg/kg bw/day	Clear dose-dependent teratogenic effects (increased number of skeletal and visceral malformations)	BASF AG (1984) Hellwig et al. (1991)

B.5.10. Other effects/information

B.5.10.1. SCOEL recommendation

Recommendation from the Scientific Committee on Occupational Exposure Limits (SCOEL, 2006):

"Dimethylformamide induces liver damage in man and in experimental animals. In a 2-year inhalation study, 25 ppm was the NOAEL for rats and the LOAEL for mice with minimal effects on the liver (Malley et al., 1994). A benchmark dose calculation resulted in a BMDL of 7.8 and a BMD of 14.7 ppm for male and female mice combined. Developmental effects are observed at higher concentrations with NOAELs for maternal and developmental toxicity of 30 ppm in rats (Lewis et al., 1992) and 50 ppm in rabbits (Hellwig et al., 1991). Irrespective of the data in animals, the effects in man are considered the best available basis for setting exposure limits. Most of the studies indicate no significant effects on liver enzymes up to 7 or 10 ppm corresponding to about 25 mg NMF/l urine. In workers without any alcohol consumption no increase in serum hepatic enzymes was observed at concentrations of 7±10 ppm, corresponding to 16±16 mg/g creatinine (about 24 mg NMF/l urine) (Wrbitzky, 1999). In combination with alcohol consumption, dimethylformamide exposure even of 7 ppm and below was reported to elicit intolerance reactions like highly visible facial flushing accompanied by other objective and subjective symptoms of discomfort. Since alcohol intolerance reactions have been

reported when alcohol was consumed after the end of the work day (Cirla et al., 1984; Lyle et al., 1979), this effect should be avoided. Sensitive individuals (about 5% of European populations and up to 90% of Asian populations) have a higher risk for alcohol intolerance reactions being reported even at concentrations of about 4 ppm. The database available, however, provides no reliable NOAEL for eliciting such alcohol intolerance reactions.

Based on the human data on liver enzymes, an OEL of 10 ppm (25 mg NMF/l urine) is considered protective provided that excessive dermal uptake and alcohol consumption are avoided. However, taking into account the results from the effects on the liver in a long-term toxicity study in mice, for which a BMDL of 7.8 ppm and BMD of 14.7 ppm was calculated, an OEL of 5 ppm is proposed. The OEL of 5 ppm also protects from developmental toxicity for which the NOEL was 50 ppm.

Dimethylformamide shows irritating properties in the eyes but not on the skin of laboratory animals. In experiments with volunteers exposed to 20 ppm dimethylformamide for 8 hours, no indications of irritation were observed. Therefore, an STEL of 10 ppm is considered to protect from local irritation.

Dermal uptake of dimethylformamide (liquid or gaseous) contributes significantly to systemic toxicity. A "skin" notation is considered necessary. Due to the significant dermal uptake of dimethylformamide, biological monitoring is highly recommended. A 8-h TWA of 5 ppm corresponds to a biological value (post-shift) of about 15 mg N-methylformamide/l urine.*

At the levels recommended, no measurement difficulties are foreseen".

* The SCOEL has agreed that there is a need to assign a skin notation if dermal absorption could contribute substantially to the total body burden and consequently to concern regarding possible health effects. "Substantial contribution" to total body burden is established on the basis of human biomonitoring studies and studies in human volunteers. According to Mráz and Nohova (1992), in case of exposure to DMF vapour, absorption via the skin and the lung were estimated to be 40.4 and 59.6 %, respectively. After direct contact with skin, DMF absorption could be equal to absorption after inhalation. It was evident in a 15-min dipping-hand-experiment, where the amount of metabolites found was as high as that seen after 8-hour inhalation exposure to DMF vapour of 60 mg/m³ (Mráz and Nohova, 1992). Besides, the resorption rates correlated positively with increased temperature and humidity. It should be noted that a skin notation relates specifically to dermal absorption of the material (whether as solid, liquid or gas), i.e. it is determined by the toxicokinetic properties of the material in relation to the level at which the OEL is established. It does not relate to and is not intended to give warning of direct effects on the skin such as corrosivity, irritation and sensitisation, criteria for which are described in Annex VI of Directive 67/548/EEC. According to worker legislation (see section B.9.1.1), employees are obliged to reduce the dermal exposure as much as possible for substances given a skin notation.

In the European Union and Switzerland, 5 ppm (15 mg/m³) is used while in Austria, Canada, USA and Japan, 10 ppm (30 mg/m³) is used.

B.5.10.2. Human information (biomonitoring studies and studies in volunteers)

The information on exposure-related observations in humans related to hepatotoxicity endpoint has been taken from the registration dossier, Health Canada Report (1999) and publications freely available.

Levels of serum hepatic enzymes in populations occupationally exposed to DMF have been determined in several cross-sectional studies.

Cirla et al., 1984

Cirla et al. (1984) reported a significant increase in serum enzymes in 100 workers exposed to a time-weighted average (TWA) of 7 ppm (21 mg/m³) (range 3-20 ppm [9-60 mg/m³]). The mean exposure period was 5 years (range 1-15 years). The referent group was 100 workers at the same or similar factories, without exposure to any solvents or toxic metals, matched by sex, age group, alcohol

history, smoking habits, coffee intake, socioeconomic status, residence and dietary customs. Clinical evaluation was carried out and a laboratory assessment was performed for blood cell counts and serum AP, AST, ALT and gamma-GT. Serum gamma-GT was abnormally high in 25/100 exposed and only 10/100 referents ($p < 0.01$). Higher prevalences in the exposed group for abnormally high serum levels of AST (9 vs. 3) and ALT (12 vs. 8) were not statistically significant. AP values were normal in all subjects. Several symptoms, including headache, dyspepsia and digestive impairment, characteristic of effects on the liver, were also associated with exposure to DMF.

Tomasini et al., 1983

There were also increases in serum levels of hepatic enzymes in 2 of 13 workers exposed to 5-20 ppm (15-60 mg/m³) DMF (and other solvents) (Tomasini et al., 1983). Histopathological changes in the liver have also been reported in occupationally exposed workers, although quantitative data on levels of exposure are not well documented. Tomasini et al. (1983) reported hepatic pain and palpable liver in 4 of 13 workers exposed to 5-20 ppm (15-60 mg/m³) DMF (and other solvents) for periods ranging from a few weeks to 4 years. Redlich et al. (1990) carried out biopsies of liver from workers heavily exposed to DMF (and other solvents; quantitative data not reported). Workers exposed for less than 3 months had hepatocellular necrosis, enlarged Kupffer cells, microvesicular steatosis, complex lysosomes and pleomorphic mitochondria. The liver of workers exposed for longer terms (14-120 months) had fatty changes with occasional lipogranuloma.

Increases in serum enzymes were reported in follow-up studies: in 183 workers exposed to <10-60 ppm (<30-180 mg/m³) DMF (and other solvents) (Wang et al., 1991) and in a smaller group (n = 13) exposed to 10-42 ppm (30-126 mg/m³) (Yang et al., 1994 [abstract]).

Fioritto et al., 1997

Fiorito et al. (1997) observed a significant increase in serum hepatic enzyme levels in 12 of 75 workers employed in a synthetic leather factory, exposed to 7 ppm (21 mg/m³) of DMF. Serum analysis revealed that the mean values of liver function indices (ALT, AST, GGTP, AP) were significantly higher in the exposed group compared to controls, as was the percentage of workers with abnormal liver function: 17 of 75 (22.7%) had abnormal transaminase values, compared to 4% in controls.

Most of the workers (52 of 75) consumed little (< 20 g/day) or no alcohol, because alcohol use was reported to cause symptoms in the workplace. Forty percent of workers complained of disulfiram-like symptoms with alcohol consumption, such as face flushing (38%), palpitation (30%), headache (22%), dizziness (22%), body flushing (15%), and tremors (14%).

The evaluation of ‘‘paired enzymes’’ using the method suggested by Wright showed that 12 of 75 subjects had abnormal ‘‘paired enzymes,’’ while 11 others had higher BA levels. To avoid confounding factors, liver function tests were analyzed in subjects positive and negative for hepatitis markers and no difference was found. Similar analyses were done stratifying by alcohol consumption. In non-, light (< 20 g/day), and heavy alcohol drinkers (20–50 g/day), there were no significant differences in transaminase values, whereas GGTP levels were higher in heavy drinkers ($P < 0.05$). Multivariate analysis confirmed that enzyme levels (ALT, AST, GGTP) are not correlated with alcohol consumption or age but are significantly correlated with DMF exposure when calculated in terms of work seniority in the factory, BMI, and serum cholesterol level ($P < 0.005$). Multiple regression analysis showed that cumulative exposure (work seniority) was the most significant factor ($P < 0.005$) in determining higher enzyme activity and was more important than serum cholesterol level (P , 0.05) and BMI ($P < 0.05$). ANCOVA revealed that ALT, AST, GGTP, and PA are significantly higher ($P < 0.001$) in exposed workers also when data are adjusted for BMI and serum cholesterol level.

Major et al., 1998

Major et al. (1998) reported an increase in serum enzymes (significance not reported) in 26 workers exposed to 0.2-8 ppm (0.6-24 mg/m³) DMF with concomitant exposure to CAN (acrylonitrile). Six of the 26 exposed subjects were hospitalized because of liver disfunction that had developed due inhalative exposure to DMF. The rate of smoking was estimated on the basis of serum thiocyanate

(SCN) levels. Average peak air ACN and DMF concentrations were over the maximum concentration limits at the time of both investigations. Urine ACN and monomethyl-formamide (MMF) excretions of the exposed subjects were almost doubled after work shifts. An increase in lymphocyte count (in months 0 and 7), and severe alterations in the liver function were observed in the exposed subjects. Repeated increases of total leukocyte counts (WBC) and urine hyppuric acid levels were detected in 10 and 13 cases, respectively; repeated increases of GPT and GGT enzyme activities were found in 11 subjects, indicating serious alterations in hematology, and in liver functions of the exposed subjects.

There were no increases in serum hepatic enzymes in 22 workers exposed to "<10 ppm" (<30 mg/m³) (Lauwerys et al., 1980), 6 workers exposed to 1-5 ppm (3-15 mg/m³) (Yonemoto and Suzuki, 1980), 28 workers exposed to a mean concentration of 6 ppm (18 mg/m³) (Catenacci et al., 1984), 207 workers exposed to 0.1-7 ppm (0.3-21 mg/m³) (Cai et al., 1992) or 126 workers exposed to up to 2.3 ppm (6.9 mg/m³) (Wrbitzky, 1999).

Lauwerys et al., 1980

Two studies were carried out among workers exposed to dimethylformamide (DMF) in an acrylic fiber factory The first study involved 22 exposed workers and 28 control workers in whose measurements of hepatic enzymes were performed on Monday and Friday morning. The values exceeding shightly the upper normal limit as defined for an adult population and the mean value of the various parameters were not significantly different between the two groups. Furthermore, the differences between the Monday and the Friday individual results did not differ between the exposed and the control groups and when the exposed workers were classified into two subgroups according to their integrated exposure to DMF vapour during the 5-day observation period (above or below 300 mg/m 3 x h) no significant difference between the two subgroups was found One can therefore conclude that exposure to DMF vapour for 5 years at a level usually below 30 mg/m³ does not seem to entail a risk of liver cytolysis It should be stressed, however, that in this factory, the selection criteria at the beginning of employment are rather severe. Nevertheless, despite the apparently "safe" exposure conditions, some workers reported experiencing signs of alcohol intolerance (antabuse effect) at the end of the day when they had been exposed to peak concentrations of DMF vapour (e g , during spinneret cleaning) This indicates that interference with alcohol metabolism still occurs at an exposure level below that causing liver cytolysis.

Yonemoto and Suzuki, 1980

Exposure of DMF (dimethylformamide) and urinary MF (methylformamide- metabolite of DMF) were measured in nine male workers handling surface-treating agents containing DMF for 5 consecutive days The result of liver function tests (SGOT, SGPT, ALP, y-GTP) of workers conducted half-yearly for 3 years had been in the normal range. Among 11 workers of this section, six claimed that they were less tolerant to alcohol beverages than before But nobody had experienced typical episodes of alcohol intolerance due to DMF.

Catenacci et al., 1984

Catenacci et al. (1984) investigated liver function (serum glutamate-oxaloacetate transaminase [SGOT], serum glutamate-pyruvate transaminase [SGPT], gamma-GT and AP) in workers employed for at least 5 years in an acrylic fibre plant. The first group of 28 subjects worked in the spinning department, where DMF exposure (8-hour TWA) ranged from 12 to 25 mg/m³ (4 to 8 ppm), with a mean of 18 mg/m³ (6 ppm). The second group consisted of 26 subjects exposed, in the polymer department, to DMF at (8-hour TWA) 1.8-5 mg/m³ (0.6-1.8 ppm), with a mean of 3 mg/m³ (1 ppm). A control group consisted of 54 subjects matched for age, smoking/alcohol consumption and history of liver disease, who had never been occupationally exposed to solvents. Mean serum values for SGOT, SGPT, gamma-GT and AP did not differ among the three groups and were within the normal ranges.

Cai et al., 1992 (abstract)

A factory survey was conducted in a plant where N,N-dimethylformamide (DMF) was in use during the production of polyurethan plastics and related materials In all, 318 DMF-exposed workers (195 men and 123 women) and 143 non-exposed controls (67 men and 76 women) were examined for

time-weighted average exposure (to DMF and other solvents by diffusive sampling), hematology, serum biochemistry, subjective symptoms, and clinical signs Most of the exposed workers were exposed only to DMF, whereas others were exposed to a combination of DMF and toluene DMF exposure in the former group was up to 7 0 ppm (geometric mean on a workshop basis), whereas it was up to 2 1 ppm in combination with 4 2 ppm toluene Both hematology and serum biochemistry, results (including aspartate and alanine aminotransferases, y-glutamyl transpeptidase and amylase) were essentially comparable among the 3 groups. There was, however, a dose-dependent increase in subjective symptoms, especially during work, and in digestive system-related symptoms such as nausea and abdominal pain in the past 3-month period The prevalence rate of alcohol intolerance complaints among male (assumedly) social drinkers was also elevated in relation to DMF dose.

Wrbitzky, 1999

In a factory producing synthetic fibers the hepatotoxic effects of DMF were investigated in 126 male employees, especially with regard to the combination effects of DMF exposure and ethyl alcohol consump- tion. A collective of similar structure from the same factory served as a control collective. The DMF concentrations in the air ranged from <0.1 (detection limit) to 37.9 ppm (median 1.2 ppm). The results indicate a statistically signifcant toxic infuence of DMF on liver function. Alcohol has a synergistic e dependent factors of DMF and those of alcoho workplace conditions the hepatotoxic effects of alcohol are more severe than those of DMF. In the exposed group there was a statistically signifcantly greater number of persons who stated that they had drunk less since the beginning of exposure (13% versus 0). This corresponded with the data on symptoms occurring after alcohol consumption (71% versus 4%). In the work areas with lower-level exposure to DMF there was greater alcohol consumption. It corresponded to that of the control collective not exposed to DMF.

Summary of effects on the liver (Health Canada, 1999)

While there have been considerable variations in the size of study populations, magnitude and duration of exposure, extent of exposure to other substances and adequacy of reporting in these investigations, there is a consistent pattern of increase in serum enzymes in workers with relatively higher exposures in the studies, some of which included individual monitoring. In summary, the results concerning exposure-response are consistent across studies, with increases in serum hepatic enzymes not being observed at concentrations in the range of 1-6 ppm (3-18 mg/m³). At higher levels of exposure (> 7 ppm [>21 mg/m³]), increased serum levels of hepatic enzymes have been observed consistently. Women were excluded from analyses because of the small numbers.

Generally, when serum levels of liver transaminases were raised, the AST/ALT ratio was <1, an indication that abnormal function was not due to alcoholic liver disease (Redlich et al., 1988; Fleming et al., 1990).

B.5.11. Derivation of DNEL(s)/DMEL(s)

The calculation of the DNELs is performed in accordance with the principles given in ECHA (2012) “Guidance of Information Requirements and Chemical Safety Assessment, Chapter R.8.

B.5.11.1. Overview of typical dose descriptors for all endpoints

Table B59. Available dose-descriptor(s) per endpoint as a result of its hazard assessment.

Endpoint	Route	Dose descriptor or qualitative effect characterisation; test type	Reference to selected study (see footnotes for justification)
Acute toxicity	oral	LD_{50}: 3010 mg/kg bw	
Acute toxicity	dermal	LD_{50}: 3160 mg/kg bw	
Acute toxicity	inhalation	LC_{50}: 5900 mg/m³	

Endpoint	Route	Dose descriptor or qualitative effect characterisation; test type	Reference to selected study (see footnotes for justification)
Irritation / Corrosivity	skin	No adverse effect observed (not irritating)	
Irritation / Corrosivity	eye	Adverse effect observed irritating	
Sensitisation	skin	No adverse effect observed (not sensitising)	
Sensitisation	respiratory tract	No adverse effect observed (not sensitising)	
Repeated dose toxicity	oral	NOAEL: 238 mg/kg bw/day (subacute; rat) Target organs: digestive: liver	
Repeated dose toxicity	inhalation (systemic effects)	NOAEC: 80 mg/m³ (chronic; rat) Target organs: digestive: liver	
Mutagenicity	*in vitro* / *in vivo*	No adverse effect observed (negative)	see section 5.7.1 / 5.7.2
Reproductive toxicity: effects on fertility	oral	NOAEL = 219 mg/kg bw/day	
Reproductive toxicity: effects on fertility	dermal	NOAEL = 200 mg/kg bw/day	
Reproductive toxicity: effects on fertility	inhalation	NOAEC = 150 mg/m³	
Reproductive toxicity: developmental toxicity	oral	NOAEL = 219 mg/kg bw/day	
Reproductive toxicity: developmental toxicity	dermal	NOAEL = 200 mg/kg bw/day	
Reproductive toxicity: developmental toxicity	inhalation	NOAEC = 150 mg/m³	

B.5.11.2. Selection of the DNEL(s) or other hazard conclusion for critical health effects

Table B60. Hazard conclusions for workers.

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects - Long-term	DNEL (Derived No Effect Level): 15 mg/m³	repeated dose toxicity (By inhalation)
Inhalation	Systemic effects - Acute	DNEL (Derived No Effect Level): 30 mg/m³	acute toxicity (By inhalation)
Inhalation	Local effects - Long-term	DNEL (Derived No Effect Level): 15 mg/m³	repeated dose toxicity
Inhalation	Local effects - Acute	DNEL (Derived No Effect Level): 30 mg/m³	acute toxicity
Dermal	Systemic effects - Long-term	DNEL (Derived No Effect Level): 0.79 mg/kg bw/day	repeated dose toxicity
Dermal	Systemic effects - Acute	DNEL (Derived No Effect Level): 6.3 mg/kg bw/day	acute toxicity (Dermal)
Dermal	Local effects - Long-term	DNEL (Derived No Effect Level): 267 µg/cm²	repeated dose toxicity
Dermal	Local effects - Acute	DNEL (Derived No Effect Level): 3600 µg/cm²	acute toxicity
Eyes	Local effects	Low hazard (no threshold derived)	

Further explanations on hazard conclusions:

- **Inhalation Systemic effects - Long-term:** DNELs derived from NOAELs obtained in different repeated dose toxicity inhalation studies of different duration (sub-acute, sub-chronic and chronic as well in reproductive toxicity studies) are similar to the existing OEL value. Therefore, OEL value is used.

- **Inhalation Systemic effects - Acute:** OEL value is taken as a DNEL because a measured value is of higher priority compared to a calculated one. Moreover, derived DNELs from a lot of NOAELs obtained in animal studies are similar with this value.

- **Inhalation Local effects - Long-term:** OEL value ensures that local effects will not occur.

- **Inhalation Local effects - Acute:** OEL value ensures that local effects will not occur.

- **Dermal Systemic effects - Long-term:** Dermal penetration of DMF can play a significant role in the systemic toxicity of this substance. Therefore, a qualitative control of risk is more appropriate in this case (see RMMs). Semi-quantitative approach: an oral NOAEL of 238 mg/kg bw is the dose descriptor starting point (BASF, 1977, XXII 402). No modification of the starting point performed. AFs are: 4 (interspecies) x 2.5 (interspecies differences in toxicodynamics) x 5 (intra-species) x 6 (sub-acute to chronic).

- **Dermal Systemic effects - Acute:** In a various studies, short-term dermal exposure led to significant penetration rates of DMF through the skin. Therefore, a qualitative control of risk is

more appropriate in this case (see RMMs). Semi-quantitative approach: a LD_{50} value of 3160 mg/kg bw was used as a dose descriptor starting point (TSCATS: OTS 0516779, 1978). No modification of the starting point necessary. AFs are: 4 x 5 x 10 x 2.5.

- **Dermal Local effects - Long-term:** Dermal exposure provides a substantial contribution to the total body burden of DMF. Therefore, a qualitative control of risk is more appropriate in this case (see RMMs). Semi-quantitative approach: an oral rat NOAEL of 238 mg/kg bw is the dose descriptor starting point (BASF, 1977, XXII/401). Modification of the starting point: (NOAEL (238 mg/kg bw) x (0.25 kg/44.5 m²) = 1.34 mg/cm². AF is: 5 (intraspecies).

- **Dermal Local effects - Acute:** In a various studies, short-term dermal exposure led to significant penetration rates of DMF through the skin. Therefore, a qualitative control of risk is more appropriate in this case (see RMMs). Semi-quantitative approach: DNEL = (NOAEL (3160 mg/kg bw) x (0.25 kg/44.5 m²)) /5 (intra-species) (TSCATS: OTS 0516779, 1978).

- **Eyes Local effects:** According to ECHA REACH Guidance Part E: Risk Characterisation (Version 2.0, November 2012) and the applied classification as Eye Irritant (Category 2), the hazard is considered as low.

Table B61. Further explanation on DNEL derivation for workers.

Route / Type of effect	DNEL derivation	Assessment factors (AF) for DNEL derivation
Inhalation Systemic effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** OEL value 15 mg/m³	
Inhalation Systemic effects - Acute	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** OEL 30 mg/m³ (long-term; extrapolated to acute/short-term)	
Inhalation Local effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** OEL value: 15 mg/m³	
Inhalation Local effects - Acute	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** OEL value: 30 mg/m³ (long-term; extrapolated to acute/short-term)	
Dermal Systemic effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** NOAEL 238 mg/kg bw/day	**AF for difference in duration of exposure:** 6 (default (sub-acute study).) **AF for interspecies differences (allometric scaling):** 4 (default for rats.) **AF for other interspecies differences:** 2.5 (default assessment factor for

Route / Type of effect	DNEL derivation	Assessment factors (AF) for DNEL derivation
		differences in toxicodynamic). **AF for intraspecies differences:** 5 (default for workers). **Overall Assessment Factor:** 300
Dermal Systemic effects - Acute	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** LOAEL 3160 mg/kg bw/day	**AF for dose response relationship:** 10 (conversion of LOAEL into NOAEL (the highest assessment factor was taken since 1 animal died at this dose level)) **AF for interspecies differences (allometric scaling):** 4 (default for rats.) **AF for other inetrspecies differences:** 2.5 (default assessment factor for differences in toxicodynamic) **AF for intraspecies differences:** 5 (default for workers). **Overall Assessment Factor:** 500
Dermal Local effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** NOAEL	**AF for intraspecies differences:** 3 (default for workers) **Overall Assessment Factor:** 5
Dermal Local effects - Acute	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** LOAEL: 3160 mg/kg bw/day	**AF for intraspecies differences:** 5 (default for workers). **Overall Assessment Factor:** 5

Justification for route-to-route extrapolation:

- **Inhalation Systemic effects - Long-term:** not applicable (OEL value is used)

- **Inhalation Systemic effects - Acute:** not applicable (OEL value is used)

- **Dermal Systemic effects - Long-term:** No adjustments in absorption were performed by oral-to-dermal extrapolation since absorption of DMF into the body is significant and set to 100 % for all exposure routes.

- **Dermal Systemic effects - Acute:** No adjustments in absorption were performed by oral-to-dermal extrapolation since absorption of DMF into the body is significant and set to 100 % for all exposure routes.

Discussion

The calculation of the DNELs is performed in accordance with the principles given in ECHA (2008)

"Guidance of Information Requirements and Chemical Safety Assessment, Chapter R.8: Characterisation of dose [concentration]-response for human health."

Available dose descriptors:

From all available data for the different human health endpoints it is clear that N, N-dimethylformamide (DMF) exerts its effect by a threshold mode of action. Thus, DNELs can be calculated for the different threshold endpoints based on the most relevant dose descriptors per endpoint. DNELs are derived from the available toxicity data of DMF, reflecting the routes, duration and frequency of exposure. DNELs are derived for workers and the general population. The general population includes consumers and humans exposed via the environment. There are following annotations for each endpoint:

- DNELs for acute toxicity have been derived because DMF is classified as harmful in contact with skin (H312) and harmful if inhaled (H332);

- A qualitative approach for the risk assessment of eye and respiratory tract irritation/corrosion and skin sensitization is used since no dose descriptors are available on these endpoints;

- DNELs for long-term systemic effects are derived using data from chronic inhalation toxicity study in rats (Malley et al., 1994);

For the non-threshold endpoints (mutagenicity and carcinogenicity) no DNELs can be derived because a No-Effect Level could not be established from the relevant studies. Hence, the hazard characterization is based on a qualitative approach;

- Since DMF may damage the unborn child (H360D), DNELs for the reproductive toxicity have also been derived.

In order to address the differences between toxicological effect data obtained in animal studies and the real human situation, assessment factors are applied. The function of assessment factors (AFs) is to correct uncertainties and variability within and between species in the effect data. First of all, available dose descriptors were converted into a correct starting point to take into account differences in routes of exposure between experimental animals and humans, differences in human and animal exposure conditions and possible differences in absorption between routes and between experimental animals and humans. Consecutively, the assessment factors have been applied to the corrected starting point to obtain the endpoint specific DNELs.

The assessment factors are applied in accordance with ECHA (2008) "Guidance of Information Requirements and Chemical Safety Assessment, Chapter R.8: Characterisation of dose [concentration]-response for human health".

Modification of the relevant dose descriptors to the corrected starting point:

<u>Bioavailability (absorption)</u>

Absorption of DMF into the body is significant and set to 100 % for all exposure routes. Absorption is assumed to be the same for experimental animals and humans for all exposure routes. Therefore no adjustments of starting points regarding absorption rates in animals and humans per exposure routes were performed.

100 % dermal absorption is assumed, based on the criteria set out in Annex IV-B of the EU Technical Guidance Document on Risk Assessment (TGD; 2003, Part I).

<u>Route-to-route extrapolation:</u>

No default factor (i.e. factor 1) is applied when oral-to-dermal extrapolation is performed in accordance with Section R.8.4.2 (p.25).

Exposure conditions:

Exposure times differed in the acute inhalation and repeated dose inhalation studies. The dose descriptors were corrected as described in the Appendix R.8-2.

Respiratory volumes:

Differences in the respiratory volumes between experimental animals and humans were used (allometric scaling factor) as well as differences in the respiratory volumes by light activity in workers.

Applying of assessment factors:

Interspecies differences:

An assessment factor for interspecies differences includes a factor for allometric scaling and for remaining interspecies difeferences. “Allometric scaling extrapolates doses according to an overall assumption that equitoxic doses (when expressed in mg/kg bw/day) scale with body weight to the power of 0.75.” To extrapolate doses used in rat studies to equivalent doses in humans an assessment factor of 4 for allometric scaling is applied (Table R. 8-3). Regarding the assessment factor for remaining interspecies differences, “if no substance-specific data are available, the standard procedure for threshold effects would be, as a default, to correct for differences in metabolic rate (allometric scaling) and to apply an additional factor of 2.5 for other interspecies differences, i.e. toxicokinetic differences not related to metabolic rate (small part) and toxicodynamic differences (larger part)” (section R.8.4.3.1). Therefore the cumulative assessment factor for interspecies differences amounts to 10 (4 x 2.5).

The assessment factor for interspecies differences is applied in case of DNEL derivation for oral and dermal routes.

No species-specific default assessment factor for allometric scaling is applied in case of inhalation exposure routes in animals which were taken to assess human inhalatory exposure. This is due to the fact that “doses in experimental animal studies expressed as concentrationsas are assumed to be already scaled according to the allometric principle, since ventilation rate and food intake directly depend on the basal metabolic rate” (section R.8.4.3.1). No additional assessment factors are applied for inhalation route and for local effects to obtain a corrected starting point (Table R8-4, Appendix R.8-2, part 2, example A1/B2).

In deriving of dermal irritation DNELs no allometric scaling is applied because of local effects (Section R.8.4.3.1., S.31-32 and Appendix R.8-9, p.119).

Intra-species differences:

Assessment factors of 5 and 10 are applied for workers and general population, respectively, for all endpoints and all exposure routes. These assessment factors cover variations in human population because “humans differ in sensitivity to toxic insult due to a multitude of biological factors such as genetic polymorphism affecting e.g. toxicokinetics/metabolism, age, gender, health status and nutritional status. These differences can be the result of genetic and/or environmental influences. This intraspecies variation is greater in humans than in the more inbred experimental animal population.” (section R.8.4.3.1)

Extrapolation of duration: To extrapolate exposure duration from short-term (sub-acute) or sub-chronic studies to chronic exposure (a real case for workers and general population) appropriate assessment factors from Table R.8-5 are applied.

Issues related to dose response: factor of 1 in case of clear dose response was observed in an animal study.. In case of LOAEL to NOEL extrapolation, factors in the range of 3 to 10 (case-by case) were applied.

Quality of data base: factor of 1. The data base is sufficiently extensive for DMF.

Additional assessment factors:

Acute toxicity:

An uncertainty factor of 100 was applied to cover all possible effects based on the criteria given in Appendix R.8-8 of ECHA REACH Guidance R.8.

Reproductive toxicity:

An additional assessment factor of 2 in relation to qualitative and quantitative uncertainties in a variety of studies as well as severity of effects is applied in order to protect an unborn child against possible developmental toxicity (refer to ECHA REACH Guidance R.8, Appendix R. 8-12).

DNELs derivation

For workers, DNELs are needed for chronic exposure by the inhalation and dermal exposure routes.

Acute short-term exposure- systemic effects (dermal):

LD_{50} value from an acute dermal toxicity study (TSCATS: OTS 0516779, 1978) is taken as the starting point for the DNEL derivation.

The dermal $LD_{50}$of 3160 mg/kg bw, obtained in the animal study, was not modified to the corrected starting point. At this dose level, 1/4 animals died. No percutaneous irritation, no clinical signs of toxicity, no findings at necropsy suggest that 3160 mg/kg bw is a LOAEL.

DNEL = 3160/ (4 x 5 x 10 x 2.5) = 6.3 mg/kg bw. Assessment factors are: 4 – interspecies, 3 – intra-species (a default assessment factor for variability in worker's population), 10 - dose-response (LOAEL to NOEL extrapolation), 2.5 – interspecies differences in toxicodynamic. The total AF amounts to 500.

Acute short-term exposure- systemic effects (inhalation):

$LC_{50}$of 5900 mg/m³ from an acute inhalation study (BASF, 1979 (78/652)) is used for the DNEL derivation.

The LC_{50} value was modified to the corrected starting point as follows:

Corrected LC_{50} = LC_{50} x (4/0.25) ^0.333) x (6.7/10).

DNEL = (5900 x (4/0.25) ^0.333) x (6.7/10) / 5 x 100 = 19.9 mg/m³. Assessment factors are: 5 – intraspecies (a default assessment factor for variability in worker's population) ; an assessment factor of 100 is used for severity of effect to the LC_{50} value (as suggested in Box 5 of Appendix R.8-8 of above mentioned guidance document). No assessment factor for interspecies differences (for allometric scaling) is applied because of inhalation route of exposure . The total AF amounts to 500.

Due to the high uncertainties of factor 100, the OEL value is used as a DNEL to cover this endpoint. An Occupational Exposure Limit (OEL) of 5 ppm (15 mg/m³) currently exists in Germany (MAK, SCOEL) as well as in other regions of the European Union. ***This value covers both acute and the long-term systemic exposure.** This value can be exceeded on a short time base by a factor of 2 (10 ppm/30 mg/m³) and thus covers in addition the short time acute exposure. These values are also reflected by the AGW/TLV. A scientific justification is required according to the REACH guidance and understood as prerequisite to use such a value. The underlying effect observed is hepatotoxicity, but the value is also intended to prevent local effects as well as potential toxicity to reproduction (see below). Moreover, the calculated DNEL of 19.9 mg/m³ (please see above) from animal data is very similar to 15 mg/m³.

Acute short-term exposure- local effects (dermal):

NOAEL is identified using acute dermal toxicity data (LD_{50} > 3160, no findings for local effects: no irritation, TSCATS: OTS 0516779, 1978).

The conversion of the acute dermal rat NOAEL into a corrected skin irritation NOAEL was performed as described in the ECHA REACH Guidance R.8, Appendix R.8-9, Section "Modification of the dose descriptor". The dose in mg/kg bw /day was converted into mg/cm^2/day to enable the comparison with the human exposure. Skin $NOAEL_{modified}$ is calculated as following: corrected NOAEL = NOAEL test (3160 mg/kg bw) x (0.25/ 44.5 cm²) = 17.8 mg/cm² where 0.25 is average weight of rats (kg) and 44.5 is approximately 10 % of the total body surface of rats (in cm^2). No allometric scaling is applied because of local effects since the mechanism of skin irritation is considered to be same in experimental animals and in human (ECHA REACH Guidance, Section R.8.4.3.1., p.31-32 and Appendix R.8-9, p.119).

DNEL = (3160 x (0.25/44.5)) / 5 = 3.6 mg/cm². Assessment factors are: 5 - intra-species. No additional assessment factor is used. The assessment factor for allometric scaling is not appropriate in case of local effects. The total AF amounts to 5.

Long-term exposure systemic effects (dermal):

Oral rat NOAEL of 238 mg/kg bw from an oral sub-acute study (BASF, 1977, XXII/402) is used for the DNEL derivation.

The conversion of the oral rat NOAEL obtained in the animal study into a corrected dermal NOAEL was not necessary (Appendix R.8-2, Example A.1), assuming that there are no differences in oral and dermal absorption between rats and humans (worst case).

DNEL = 238/ (4 x 5 x 6 x 2.5) = 0.79 mg/kg bw/day. Assessment factors are: 4 – interspecies, 5 – intra-species, 6 - duration of exposure (sub-acute study), 2.5 – interspecies differences in toxicodynamic. The total AF amounts to 300.

The calculated DNEL is only relevant for dermal exposure route, given that inhalation exposure route is excluded. Due to the substantial absorption of DMF vapour and liquid through the skin (about 40 % of totally internal DMF based on the study results of metabolites of DMF); a dermal DNEL is a very critical point. Taking into account body weight of 70 kg for workers, dermal DNEL of 0.79 mg/kg bw corresponds to 55.3 mg DMF per person. This amount corresponds to 59 µL (by density of 0.94 g/mL). It means that dermal exposure to a few drops of DMF, which are resorbed for 100 %, will lead to exceeding of a "safe" internal dose level for workers. The "safe" internal dose level results in 2.1 mg/kg bw/day for workers since by an exposure to 5 ppm (15 mg/m³), that is SCOEL value, a 70-kg worker inhales around 150 mg DMF (standard respiratory volume of workers under light activity is 10 m³ during 8 hours). The internal dose of 2.1 mg/kg bw can be exceeded significantly in case of additional skin contact what is, in principle, the most typical exposure situation in factories. This way, the dermal DNEL of 0.79 mg/kg bw covers accidental and unintended splashing only, if the systemically absorbed dose would not exceed 2.1 mg/kg bw/day. Therefore, for dermal exposure route, a qualitative approach for the risk characterization is an additional measure to ensure a safety use of the chemical. Assuming that DMF exposed workers wear DMF-impermeable gloves, the dermal exposure route would be minimized.

Qualitative assessment of dermal exposure

Based on results of several studies it can be concluded that DMF-exposed workers should wear DMF-impermeable gloves.

Long-term exposure systemic effects (inhalation):

The existing OEL value of 5 ppm for the inhalation DNEL is proposed to be used on the basis of the following:

DNELs derived from various animal data obtained in different repeated dose toxicity inhalation

studies of different duration (acute, sub-acute, sub-chronic and chronic as well in reproductive toxicity studies) are similar to the existing OEL. For instance, using a starting point of the NOAEC from the 2-year rat study of 80 mg/m³ (Malley et al., 1994) and adjusting the NOAEC for the difference in respiratory volume for humans to rats yields the following calculation:

80 mg/m³ x (6h/8h) x (6.7m³/10m³) = 40.2 mg/m³

These two adjustments take already into consideration the interspecies allometric scaling factor, additional adjustments for species difference in absorption and metabolism are not required since the route of exposure was inhalation, and since metabolism and kinetics have been shown to be similar in rats and humans. An assessment factor of 5 for intra-species variability is applied, resulting in **8.04 mg/m³** (40.2/5). No further assessment factors are required for database quality or study duration since the NOAEL is based on a 2 year rat study conducted according to the OECD Guideline. Since the value 8.04 mg/m³ is similar to the existing OEL value of **15 mg/m³** used in Europe and other regions globally, the existing OEL is proposed to be used as the inhalation DNEL. From a variety of studies it is clear that exposure to DMF concentrations under 10 ppm for a long term does not induce health complaints and does not lead to any significant changes of the biological parameters including hepatotoxicity. At this concentration, there was no accumulation of DMF metabolites measured.

Long-term exposure local effects -dermal:

The dose descriptor for this endpoint comes from a sub-acute oral study in rats (BASF, 1977, XXII/402). A NOAEL is identified as described in the acute/short-term exposure local effects: $NOAEL_{corrected}$ = 238 mg/kg bw x (0.25 kg/44.5 cm²) = 1.34 mg/cm²/day. No further modifications are performed. Using a factor of 5 for intra-species, a resulted DNEL is 0.267 mg/cm²/day. The assessment factor for allometric scaling is not appropriate in case of local effects.The total AF amounts to 5.

Local effects (short-term and long-term) - inhalation:

There were no compound-related lesions noted in the nose or respiratory tract for any exposure concentration in both rats and mice during the long-term inhalation study (Malley et al., 1994). Therefore, no DNELs for the local inhalation effects are needed. The existing OEL values cover sufficiently a possible respiratory hazard of DMF.

Long-term exposure-systemic (reproductive toxicity effects)

Since DMF is classified as toxic to reproduction, DNELs for fertility and developmental effects need to be derived. DNELs for reproductive toxicity effects for workers are derived for two most relevant exposure routes in humans: the dermal and inhalation exposure routes.

The principles of setting DNELs are the same as for repeated dose toxicity DNELs. For reproductive toxicity effects, additional assessment factors, characteristic for the reproductive toxicity endpoint are factors which would cover qualitative and quantitative uncertainties in available reproductive toxicity studies, a factor for sensitivity of a reproductive toxicity study and a factor for severity of effects seen at different dose levels. For DMF, a factor for qualitative and quantitative uncertainties is considered to be of 1 because of sufficient information from the whole data base on this issue. The studies taken as key studies to assess possible reproductive effects of DMF in humans are reproductive toxicity studies. They are meant to provide complete information on all aspects of reproduction and development. Therefore, a factor of 1 for sensitivity of the studies is regarded to be appropriate. The common observation from a variety of reproductive studies is that the developmental toxicity effects occur at or above dose levels associated with systemic toxicity in all species for all exposure routes. Hence, the calculated reproductive toxicity DNELs will protect both the developing offspring and the mother. A factor of 2 for severity of effects is used to account for the uncertainty related with the dose-response relationship in the available reproductive toxicity studies.

Fertility and development (dermal):

NOAEL of 200 mg/kg bw was established in the dermal developmental study for rabbits (BASF AG 84/51, 1984). No modification of the starting point is necessary because routes of exposure are the same in animals and human and the dermal absorption is assumed to be similar in animals and humans (worst case).

DNEL = 200 mg/kg bw / (2.4 x 5 x 2 x 1 x 1) = 8.3 mg/kg bw. Assessment factors are: 2.4 – interspecies (the assessment factor includes only allometric scaling for rabbits), 5 - intra-species, 2 - severity of effects (uncertainties related with dose-response). Developmental effects were observed at the highest dose level (400 mg/kg bw) and in the presence of maternal toxicity. The extent and severity of effects seen was not very marked. One dead fetus and several malformations resulted in 31 % anomalies (different from control). These findings were regarded to be independent of the compound administered. A clear NOEL was concluded to be 200 mg/kg bw for maternal and embryo-/ fetotoxicity including teratogenicity. Therefore, this additional factor of 2 will be sufficient to ensure that developmental effects would not occur. Further assessment factors used: 1 - qualitative and quantitative uncertainties; 1 - sensitivity of the study (developmental study).

No assessment factor for study duration is applied (reproductive toxicity study and assessment of reproductive toxicity effects in humans). The total AF amounts to 24.

Fertility and development (inhalation):

NOAEC of 150 mg/m³ was established in the inhalation developmental study for rabbits (BASF AG 87/586, 1989). The starting point needs to be modified for differences in exposure conditions (animals were inhaled during 6 hours) and differences in respiratory volumes in workers under normal conditions and light activity:

Corrected NOAEC = 150 mg/m³ x 6h/8h x 6.7m³/ 10m³ = 75.4 mg/m³.

DNEL = corrected NOAEC (75.4 mg/m³) / (5 x 2 x 1 x 1) = 7.5 mg/m³. Assessment factors are: 5 – intra-species, 2 - severity of effects (uncertainties related with dose-response). Embryotoxicity-/teratogenic effects were observed in fetuses at the highest dose level, which was also maternal toxic. Reduced body weight and skeletal malformations were the common observations. Further assessment factors are: 1 - qualitative and quantitative uncertainties, 1 - sensitivity of the study (developmental study). No assessment factor for interspecies differences is applied (inhalation-to-inhalation) and no assessment factor for study duration is needed (reproductive toxicity study and assessment of reproductive toxicity effects in humans). The total AF amounts to 10.

Such a DNEL is close to the existing SCOEL value of 15 mg/m³. In general, delineated DNELs from data of a variety of available reproductive toxicity studies for inhalation exposure route are similar to the SCOEL value. Giving priority to SCOEL value which is based on numerous relevant study results and exposure measurements, SCOEL value is proposed as the appropriate value of protection against possible developmental toxicity. This value is sufficient to ensure that adverse reproductive toxicity effects do not occur.

Moreover, the calculated reproductive toxicity DNELs of 8.3 and 7.5 mg/kg bw/day for dermal and inhalation exposure route, respectively, are higher than those for common systemic toxicity by long-term exposure (0.79 mg/kg bw/day for dermal and 2.1 mg/kg bw/day (derived from SCOEL value of 15 mg/m³) inhalation). Therefore, the SCOEL value is sufficient that at this level reproductive toxicity effects do not occur.

* Deutsche Forschungsgemeinschaft (DFG), Senatskommission zur Prüfung Gesundheitsschädlicher Arbeitsstoffe (1992): "MAK- und BAT-Werte-Liste: maximale Arbeitsplatzkonzentrationen und biologische Arbeitsstofftoleranzwerte". Weinheim: Wiley-VCH, ISSN-Nr. 0417-1810, 40. Lieferung (2006): N, N-Dimethylformamide.

Selected DNELs

The leading health effect is hepatotoxicity and reproductive toxicity. The following DNELs are the lowest DNELs for the respective exposure routes ensuring that these effects do not occur:

DNEL systemic inhalation (short-term and long-term) =**15 mg/m³(OEL value)**
DNEL systemic dermal (long-term) = **0.79 mg/kg bw**.

Table B62. Hazard conclusions for the general population.

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects - Long-term	DNEL (Derived No Effect Level): 15 mg/m³	repeated dose toxicity (By inhalation)
Inhalation	Systemic effects - Acute	DNEL (Derived No Effect Level): 30 mg/m³	acute toxicity (By inhalation)
Inhalation	Local effects - Long-term	DNEL (Derived No Effect Level): 15 mg/m³	repeated dose toxicity
Inhalation	Local effects - Acute	DNEL (Derived No Effect Level): 30 mg/m³	acute toxicity
Dermal	Systemic effects - Long-term	DNEL (Derived No Effect Level): 0.4 mg/kg bw/day	repeated dose toxicity (Oral)
Dermal	Systemic effects - Acute	DNEL (Derived No Effect Level): 3.2 mg/kg bw/day	acute toxicity (Dermal)
Dermal	Local effects - Long-term	DNEL (Derived No Effect Level): 134 µg/cm²	repeated dose toxicity
Dermal	Local effects - Acute	DNEL (Derived No Effect Level): 1780 µg/cm²	acute toxicity
Oral	Systemic effects - Long-term	DNEL (Derived No Effect Level): 0.4 mg/kg bw/day	repeated dose toxicity (Oral)
Oral	Systemic effects - Acute	DNEL (Derived No Effect Level): 1.2 mg/kg bw/day	acute toxicity (Oral)
Eyes	Local effects	Low hazard (no threshold derived)	

Further explanation on hazard conclusions:

- **Inhalation Systemic effects - Long-term:** DNELs derived from NOAELs obtained in different repeated dose toxicity inhalation studies of different duration (sub-acute, sub-chronic and chronic as well in reproductive toxicity studies) are of similar order of magnitude to the existing OEL value. Therefore OEL value is used.

- **Inhalation Systemic effects - Acute:** OEL value is taken as a DNEL because a measured value is of higher priority compared to a calculated one. Moreover, derivated DNELs from a lot of NOAELs obtained in animal studies are similar with this value.

- **Inhalation Local effects - Long-term:** OEL value ensures that local effects will not occur.

- **Inhalation Local effects - Acute:** OEL value ensures that local effects will not occur.

- **Dermal Systemic effects - Long-term:** Dermal penetration of DMF can play a significant role in the systemic toxicity of this substance. Therefore, a qualitative control of risk is more appropriate in this case (see RMMs). Semi-quantitative approach: an oral NOAEL of 238 mg/kg bw is the dose descriptor starting point (BASF, 1977, XXII 402). No modification of the starting point performed. AFs are: 4 (interspecies) x 2.5 (interspecies differences in toxicodynamics) x 10 (intraspecies) x 6 (subacute to chronic).

- **Dermal Systemic effects - Acute:** In a various studies, short-term dermal exposure led to significant penetration rates of DMF through the skin. Therefore, a qualitative control of risk is more appropriate in this case (see RMMs). Semi-quantitative approach: a LD_{50} value of 3160 mg/kg bw was used as a dose descriptor starting point (TSCATS: OTS 0516779, 1978). No modification of the starting point necessary. AFs are: 4 x 2.5 x 10 x 10.

- **Dermal Local effects - Long-term:** Dermal exposure provides a substantial contribution to the total body burden of DMF. Therefore, a qualitative control of risk is more appropriate in this case (see RMMs). Semi-quantitative approach: an oral rat NOAEL of 238 mg/kg bw is the dose descriptor starting point (BASF, 1977, XXII/401). Modification of the starting point: (NOAEL (238 mg/kg bw) x (0.25 kg/44.5 m^2) = 1.34 mg/cm^2. AF is: 10 (intraspecies).

- **Dermal Local effects - Acute:** In a various studies, short-term dermal exposure led to significant penetration rates of DMF through the skin. Therefore, a qualitative control of risk is more appropriate in this case (see RMMs). Semi-quantitative approach: DNEL = (NOAEL (3160 mg/kg bw) x (0.25 kg/44.5 m^2)) /10 (intraspecies) = 1780 µg/cm^2 (TSCATS: OTS 0516779, 1978).

- **Oral Systemic effects - Long-term:** No modification of the starting point regarding absorption rates in animals and humans were performed. Absorption of the target substance into the body is significant via all exposure routes (set to 100 %) and considered to be the same in animals and humans. AFs are: 4 (interspecies) x 2. 5 (interspecies differences in toxicodynamics) x 10 (intraspecies) x 6 (subacute to chronic).

- **Oral Systemic effects - Acute:** The DNEL derived from LD_{50} obtained in an acute oral toxicity study is too uncertain since LD_{50} is based on mortality. Therefore the DNEL is set by multiplying of the long-term DNEL with factor of 3.

- **Eyes Local effects:** According to ECHA REACH Guidance Part E: Risk Characterisation (Version 2.0, November 2012) and the applied classification as Eye Irritant (Category 2), the hazard is considered as low.

Table B63. Further explanation on DNEL derivation for the general population.

Route / Type of effect	DNEL derivation	Assessment factors (AF) for DNEL derivation
Inhalation Systemic effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** OEL value: 15 mg/m^3	
Inhalation Systemic effects - Acute	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** OEL value: 30 mg/m^3 (long-term;	

Route / Type of effect	DNEL derivation	Assessment factors (AF) for DNEL derivation
	extrapolated to acute/short-term)	
Inhalation Local effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** OEL value: 15 mg/m³	
Inhalation Local effects - Acute	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** OEL value: 30 mg/m³ (long-term; extrapolated to acute/short-term)	
Dermal Systemic effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** NOAEL 238 mg/kg bw/day	**AF for difference in duration of exposure:** 6 (default (sub-acute study).) **AF for interspecies differences (allometric scaling):** 4 (default for rats.) **AF for other interspecies differences:** 2.5 (default assessment factor for differences in toxicodynamic) **AF for intraspecies differences:** 10 (default for general population) **Overall Assessment Factor:** 600
Dermal Systemic effects - Acute	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** LOAEL 3160 mg/kg bw/day	**AF for dose response relationship:** 10 (conversion of LOAEL into NOAEL (the highest assessment factor was taken since 1 animal died at this dose level)) **AF for interspecies differences (allometric scaling):** 4 (default for rats) **AF for other interspecies differences:** 2.5 (default assessment factor for differences in toxicodynamics). **AF for intraspecies differences:** 10 (default for general population) **Overall Assessment Factor:** 1000
Dermal Local effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** NOAEL	**AF for intraspecies differences:** 10 (default for general population) **Overall Assessment Factor:** 10
Dermal Local effects - Acute	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:**	**AF for intraspecies differences:** 10 (default for general population) **Overall Assessment Factor:** 10

Route / Type of effect	DNEL derivation	Assessment factors (AF) for DNEL derivation
	LOAEL	
Oral Systemic effects - Long-term	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** NOAEL	**AF for difference in duration of exposure:** 6 (default (sub-acute study).) **AF for interspecies differences (allometric scaling):** 4 (default for rats.) **AF for other interspecies differences:** 2.5 (default assessment factor for differences in toxicodynamics) **AF for intraspecies differences:** 10 (default for general population) **Overall Assessment Factor:** 600
Oral Systemic effects - Acute	**DNEL derivation method:** ECHA REACH Guidance **Dose descriptor starting point:** NOAEL	Multiplication of dermal long-term DNEL by a factor of 3.

Justification for route-to-route extrapolation:

- **Inhalation Systemic effects - Long-term:** not applicable (OEL value is used)

- **Inhalation Systemic effects - Acute:** not applicable (OEL value is used)

- **Dermal Systemic effects - Long-term:** No adjustments in absorption were performed by oral-to-dermal extrapolation since absorption of DMF into the body is significant and set to 100 % for all exposure routes.

- **Dermal Systemic effects - Acute:** No adjustments in absorption were performed by oral-to-dermal extrapolation since absorption of DMF into the body is significant and set to 100 % for all exposure routes.

- **Oral Systemic effects - Long-term:** No route-to-route extrapolation is needed (oral study and oral exposure in humans).

- **Oral Systemic effects - Acute:** No route-to-route extrapolation is needed (oral study and oral exposure in humans).

Discussion

There are no consumer uses for N-dimethylformamide. DNELs are derivated only for purposes of environmental risk assessment (man exposed via environment).

The principles of the DNEL calculation for the general population are the same as already described for workers. However, there are additional considerations or deviations for:

Modification of the starting point:

Bioavailability (absorption):

Since DNELs for oral route of exposure are needed, an assessment of oral absorption is relevant for the target substance. The oral absorption in rats and in humans is assumed to be extensive and the same since no substance information for oral absorption for the target substance in rats and in humans is available.

Respiratory volumes:

No differences in the respiratory volumes under normal conditions and by light activity in humans were taken into account. Exposure duration of 24 hours was used in case of inhalation exposure.

Applying of assessment factors:

A higher assessment factor of 10 (in place of 5 for workers) for intra-species variation/differences of human population was used. An assessment factor of 2.5 for remaining differences in toxicodynamics is used as well.

Calculation of endpoint-specific DNEL for general population

Long-term exposure - systemic effects (inhalation):

The inhalation NOAEC of 80 mg/m³ obtained in a chronic inhalation study in rats (Malley et al., 1994) was modified regarding duration of exposure:

Corrected inhalation NOAEC = NOAEC x (6h/d/ 24h/d), where 6 hours and 24 hours are exposure durations for experimental animals and humans per day, respectively.

Corrected Inhalation NOAEC = 80 mg/ m³ x (6/24) = 20 mg/m³

DNEL = 20 mg/m³/ (1 x 1 x 10 x 1 x 1 x 1) = 2.0 mg/m³.

Assessment factors are: 1 – interspecies (in case of inhalation exposure), 1 – differences in toxicodynamics (in case of inhalation exposure), 10 – intra-species, 1 – study duration (chronic study), 1 – dose response (clear dose response), 1 – quality of data base (default). The total AF amounts to 10.

Since an uncertainty exists calculating DNEL by default approach, the existing OEL value of 15 mg/m³ is proposed for man exposed via environment (the same as in case for workers).

Acute short-term exposure- systemic effects (inhalation):

LC_{50} of 5900 mg/m³ from an acute inhalation study (BASF, 1979 (78/652)) is used for the DNEL derivation.

The LC_{50} value was modified to the corrected starting point as follows:

Corrected LC_{50} = LC_{50} x (4/0.25) ^0.333).

DNEL = (5900 x (4/0.25) ^0.333) / (10 x 100) = 14.9 mg/m³. Assessment factors are: 10 – intra-species. An assessment factor of 100 is used for severity of effect to the LC_{50} value (as suggested in Box 5 of Appendix R.8-8 of above mentioned guidance document). No allometric scaling factor for inhalation is used. The total AF amounts to 100.

The calculated DNEL is similar to the existing OEL of 30 mg/m³ for short-term exposures. Therefore, the OEL value is proposed as DNEL, the same as in case for workers.

Local effects (short-term and long-term) - inhalation:

There were no compound-related lesions noted in the nose or respiratory tract for any exposure concentration in both rats and mice during the long-term inhalation study (Malley et al., 1994). Therefore, no DNELs for the local inhalation effects are needed. The existing OEL values cover

sufficiently a possible respiratory hazard of DMF.

Long-term exposure - systemic effects (dermal):

The oral rat NOAEL of 238 mg/kg bw was used as dermal NOAEL since no modification regarding absorption rates via oral and dermal routes in experimental animals and humans are necessary (absorption is considered to be the same in animals and humans).

DNEL = 238 mg/kg bw/ (4 x 2.5 x 10 x 6 x 1 x 1) = 0.4 mg/kg bw.

Assessment factors are: 4 – interspecies, 2.5 – interspecies differences in toxicodynamic, 10 – intra-species, 6 – study duration (sub-acute study), 1 – dose response, 1 – quality of data base. The total AF amounts to 600.

Acute short-term exposure- systemic effects (dermal):

LD_{50} value from an acute dermal toxicity study (TSCATS: OTS 0516779, 1978) is taken as the starting point for the DNEL derivation. The LD_{50} is assumed to be a LOAEL (see Discussion for workers).

DNEL = 3160/ (4 x 2.5 x 10 x 10) = 3.2 mg/kg bw.

Assessment factors are: 4 – interspecies, 2.5 - interspecies differences in toxicodynamics, 10 - intra-species, 10 - dose-response (LOAEL to NOEL extrapolation). The total AF amounts to 1000.

Long-term exposure local effects -dermal:

The dose descriptor for this endpoint comes from a sub-acute oral study in rats (BASF, 1977, XXII/402). A NOAEL is identified as described in the acute/short-term exposure local effects: NOAELcorrected = 238 mg/kg bw x (0.25 kg/44.5 cm^2) = 1.34 mg/cm^2/day. No further modifications are performed. Using a factor of 10 for intra-species, DNEL resulted in 0.134 mg/cm^2/day. The total AF amounts to 10.

Acute short-term exposure- local effects (dermal):

NOAEL is identified using acute dermal toxicity data (LD_{50}> 3160, no findings for local effects: no irritation, TSCATS: OTS 0516779, 1978).

The conversion of the acute dermal rat NOAEL into a corrected skin irritation NOAEL is described above (see Discussion for workers).

DNEL = (3160 x (0.25/44.5)) / 10 = 1.78 mg/cm^2. Assessment factors are: 10 - intra-species. No additional assessment factor is used. The total AF amounts to 10.

Long-term exposure - systemic effects (oral):

The oral rat NOAEL of 238 mg/kg bw had not to be converted.

The oral NOAEL of 238 mg/kg bw was not modified for differences in absorption by oral route in rats and in humans since no substance- and route specific information is available: oral absorption in rat = oral absorption in humans.

DNEL = 238 mg/kg bw/ (4 x 2.5 x 10 x 6 x 1 x 1) = 0.4 mg/kg bw. Assessment factors are: 4 – interspecies, 2.5 – interspecies differences in toxicodynamics, 10 – intra-species, 6 – study duration (sub-acute study), 1 – dose response (clear dose response), 1 – quality of data base (default). The total AF amounts to 600.

Acute short-term exposure- systemic effects (oral):

LD_{50} of 3100 mg/kg bw obtained in an acute oral toxicity study (BASF, 1972, Study No. X/23) is

based on lethality (1 animal died at this dose level). Therefore the setting of the acute DNEL for oral route is considered to involve too large uncertainties. Therefore the DNEL is set by multiplying of the long-term DNEL with factor of 3 (see Box 6 in Appendix R. 8-8 of REACH guidance document).

DNEL = 0.4 x 3 = 1.2 mg/kg bw.

Fertility and development (dermal):

As described for workers, fertility and developmental DNELs are needed since the substance is classified as reproductive toxicant (Repr. Cat. 1B; H360D May damage the unborn child). Therefore, a specific DNEL is needed to ensure that the effects do not occur in humans.

NOAEL of 200 mg/kg bw was established in the dermal developmental study for rabbits (BASF AG 84/51, 1984). No modification of the starting point is necessary because routes of exposure are the same in animals and human and the dermal absorption is assumed to be similar in animals and humans (worst case).

DNEL = 200 mg/kg bw / (2.4 x 10 x 2 x 1 x 1 x 1) = 4.2 mg/kg bw

Assessment factors are: 2.4 - interspecies (rabbits), 10 – intra-species, 2 - severity of effects (uncertainties related with dose-response, see Discussion for workers), 1 – study duration (developmental study, see Discussion for workers), 1 - qualitative and quantitative uncertainties, 1 - sensitivity of the study (developmental study). The total AF amounts to 48.

Fertility and development (inhalation):

NOAEC of 150 mg/m³ was established in the inhalation developmental study for rabbits (BASF AG 87/586, 1989). The starting point needs to be modified for differences in exposure conditions (animals were inhaled during 6 hours and 24 hours is exposure time for general population).

Corrected NOAEC = 150 mg/m³ x 6h/24h = 37.5 mg/m³.

DNEL = corrected NOAEC (37.5 mg/m³) / (1 x 10 x 2 x 1 x 1 x 1) = 1.9 mg/m³. Assessment factors are: 1 – interspecies in case of inhalation exposure, 10 – intra-species; 2 - severity of effects (uncertainties related with dose-response, see Discussion for workers), 1 – study duration (developmental study, see Discussion for workers), 1 - qualitative and quantitative uncertainties, 1 - sensitivity of the study (developmental study). The total AF amounts to 20.

Fertility and development (oral):

NOAEL of 200 mg/kg bw was established in the dermal developmental study for rabbits (BASF AG 84/51, 1984). No modification of the starting point is necessary because absorption rates are considered to be significant (100 %) and the same for all routes of exposure and in animals and humans (worst case).

DNEL = 200 mg/kg bw / (2.4 x 10 x 2 x 1 x 1 x 1) = 4.2 mg/kg bw

Assessment factors are: 2.4 - interspecies (rabbits), 10 – intra-species, 2 - severity of effects (uncertainties related with dose-response, see Discussion for workers), 1 – study duration (developmental study, see Discussion for workers), 1 - qualitative and quantitative uncertainties, 1 - sensitivity of the study (developmental study). The total AF amounts to 48.

Selected DNELs

The leading health effect is hepatotoxicity and reproductive toxicity. The following DNELs are the lowest DNELs for the respective exposure routes ensuring that these effects do not occur:

DNEL systemic inhalation =**15 mg/m³(OEL value)**
DNEL systemic dermal (long term) = **0.4 mg/kg bw**

DNEL systemic oral (long-term) = **0.4 mg/kg bw**

B.6 Human health hazard assessment of physico-chemical properties

B.6.1. Explosivity

Data waiving: see CSR section 1.3 Physicochemical properties.

Classification according to CLP

Name: N, N-dimethylformamide

State/form of the substance: liquid

Reason for no classification: conclusive but not sufficient for classification

B.6.2. Flammability

Flammability

Data waiving: see CSR section 1.3 Physicochemical properties.

Flash point

The available information on flash point is summarised in the following table:

Table B64. Information on flash point.

Method	Results	Remarks	Reference
closed cup (DIN 51755) ISO DIN 51 755	Flash point: 57.5 °C at 1013.25 hPa	2 (reliable with restrictions) key study experimental result **Test material (EC name): N,N-dimethylform- amide**	BASF AG (1979b)
Determination of flash point closed cup Closed cup method	Flash point: 58 °C	2 (reliable with restrictions) supporting study Handbook data (peer reviewed database) **Test material (EC name): N,N-dimethylfor m- amide**	Clayton G.D., Clayton, F.E. (1993)
Determination of flash point closed cup	Flash point: 58 °C	2 (reliable with restrictions) supporting study	IPCS (International Programme on Chemical Safety)

Method	Results	Remarks	Reference
Closed cup method		Handbook data (peer reviewed database) **Test material (EC name): N,N-dimethylformamide**	(1991)
Determination of flash point closed cup German standard DIN 51755	Flash point: 58 °C	2 (reliable with restrictions) weight of evidence experimental result **Test material (EC name): N,N-dimethylformamide**	BASF AG (2002)
Determination of flash point closed cup Method: other: DIN 51 755	Flash point: 58 °C Remarks: Flash point = 58 °C	2 (reliable with restrictions) weight of evidence experimental result **Test material (EC name): N,N-dimethylformamide**	Bipp H., Kieczka H. (1989)

Discussion

The following sources give details regarding flash point of N, N-dimethylformamide: BASF AG (1979, 2002), Bipp, H., Kieczka, H. (1989), Clayton G. D., Clayton, F. E. (1993), and IPCS (1991).

The following information is taken into account for any hazard / risk assessment:

Flash point = 57.5 °C at 1013.25 hPa

Classification according to GHS

Name: N, N-dimethylformamide

State/form of the substance: liquid

Classification

Reason for no classification (Flammable liquids): conclusive but not sufficient for classification
Reason for no classification (Flammable gases): conclusive but not sufficient for classification

Reason for no classification (Flammable aerosols): conclusive but not sufficient for classification

Reason for no classification (Flammable solids): conclusive but not sufficient for classification

B.6.3. Oxidising potential

Data waiving: see CSR section 1.3 Physicochemical properties.

Classification according to CLP

Name: N, N-dimethylformamide

State/form of the substance: liquid

Reason for no classification (Oxidising gases): conclusive but not sufficient for classification

Reason for no classification (Oxidising liquids): conclusive but not sufficient for classification

Reason for no classification (Oxidising solids): conclusive but not sufficient for classification

B.7 Environmental hazard assessment

Considered not be relevant for this restriction dossier.

B.8 PBT and vPvB assessment

Considered not be relevant for this restriction dossier.

B.9 Exposure and risk assessment (tiered approach)

The original structure of this part of the restriction dossier was slightly modified. Due to the implementation of different assessment approaches (TIER 1 assessment, TIER 2 assessment, article assessment) in this part of the dossier, the original section B.10 (Risk characterisation) was integrated in section B.9 (Exposure assessment) of the document which is now called "Exposure and risk assessment (tiered approach)". Section B.9 was further divided in different subsections in order to clearly represent all available assessment approaches.

Due to these modifications, section B.11 (Summary on hazard and risk) is now displayed as chapter B.10.

General discussion on releases and exposure

The substance DMF was registered in 2010. The Identified Uses as well as the exposure and risk assessment in the registration dossier were updated recently (February 2014). Nevertheless, the whole risk assessment was revised in the course of this restriction proposal due to more conservative DNELs. The complete risk assessment can be found in Appendix B1.

In order to perform an adequate update of the risk assessment in the context of the REACH registration dossier update in February 2014, all identified Downstream Users of the Lead Registrant were requested to provide specific information regarding their use patterns of the substance. For this purpose, two consecutive questionnaires were provided to the Downstream Users. In accordance with the REACH Use Descriptor System, information regarding the relevant Sector of Use (SU), Product Category (PC), Article Category (AC), Process Category (PROC) and Environmental Release Category (ERC) were gained in the first questionnaire. In addition, other important assessment parameters such as tonnages, measured data, Operational Conditions (OCs) and Risk Management Measures (RMMs) for each application/process were requested via a second questionnaire. After receiving all relevant information, the description and assessment Identified Uses of the substance were revised accordingly in the CSR. Figure B1 shows the total number of companies which provided relevant information via the first questionnaire.

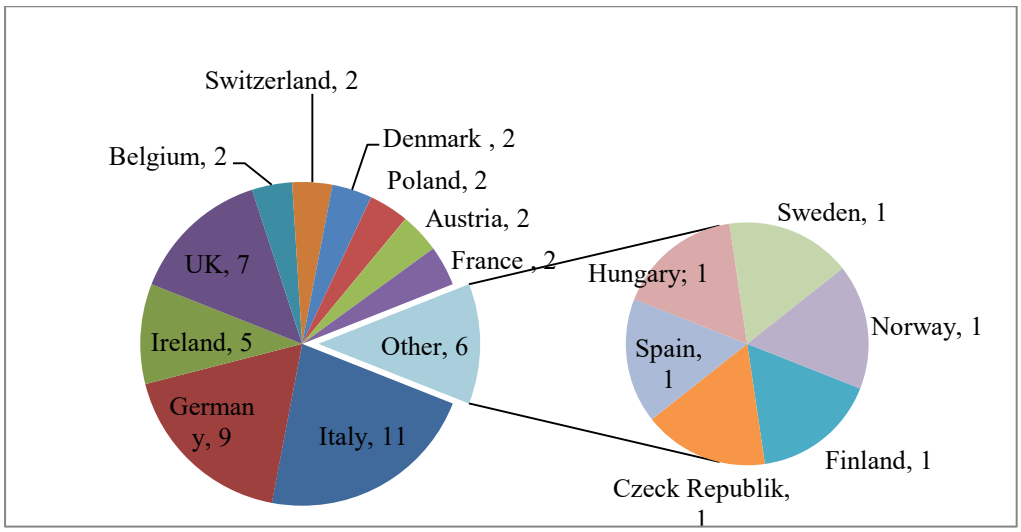


Figure B1. Total number of companies which provided exposure relevant questionnaires sorted by European countries.

The risk assessment for the substance was performed using CHESAR v2.2 (REACH registration dossier update) to assess human exposure and to predict environmental concentrations. With regard to the human health assessment, exposure calculations using CHESAR v2.2 were performed as TIER 1 approach. Due to the fact that relevant measured data from several different industrial sites is available, a TIER 2 assessment was additionally elaborated. For revision of the risk and exposure assessment in the course of this restriction dossier, CHESAR v2.3 has been used.
Due to the detailed and complex approach for this risk assessment, exposure estimations and risk characterisations take the current state of the art into account. All exposure calculations for Human Health are based on recent information on detailed process conditions provided by the relevant Downstream Users.

However, DMF residues in articles and their potential risk for industrial workers and/or consumers have not been considered in detail in the registration dossier. A human health assessment of this article service-life was consequently performed for the restriction report in order to ensure safe handling of DMF throughout its complete life-cycle including its service-life.

Summary of the existing legal requirements

Please refer to section B9.3.2 of this document.

Summary of the effectiveness of the implemented operational conditions and risk management measures

The operational conditions (OCs) and risk management measures (RMMs) implemented by the registrant in the updated registration dossier are summarized as follow:

- Concentration of substance in mixture (100 %; > 25 %; 5 – 25 %; 1 – 5 %; < 1 %)
- Duration of activity (max. 8 h; max. 4 h; max. 1 h; max. 15 min)
- General ventilation (basic; good; enhanced)
- Containment (closed; semi-closed; open)
- Local Exhaust Ventilation (yes with 80, 90 or 95 % effectiveness; no)
- Occupational Health and Safety Management System (Advanced; basic)
- Dermal protection (APF 5; APF 10; APF 20)

- Respiratory protection (APF 10, APF 20)
- Place of use (indoor; outdoor)
- Process temperature
- Skin surface potentially exposed
- Chemical goggles

Specific input parameters such as Containment, Occupational Health and Safety Management System and Skin surface potentially exposed are predefined within the CHESAR modelling tool and cannot be modified. These parameters are based on the relevant life-cycle step (manufacture, formulation, industrial use, etc.) and the relevant process category which has been used to describe a specific application of the substance.

The remaining input parameters have been selected for each individual process. The vapour pressure was calculated based on the relevant process temperature which had a significant impact on the performed calculations. The vapour pressure directly defines the fugacity class of a substance. For process temperatures ≤ 70 °C the fugacity of DNF is described as medium (Vapour pressure between 0.5 – 10 kPa). For process temperatures ≥ 80 °C the fugacity is described as high (Vapour pressure > 10 kPa). Chemical goggles need to be worn for any application to ensure safe handling of the substance (qualitative assessment).
The effectiveness and corresponding exposure reduction due to the implementation of specific OCs and/or RMMs are provided in the following table. These reduction factors are pre-implemented in the applied modelling tool CHESAR v2.2.

Table B65. Effectiveness and corresponding exposure reduction of specific OCs and RMMs.

Input parameter	Specific OC / RMM	Exposure modifying factor
Substance concentration	100 %	1
	> 25 %	1
	5 – 25 %	0.6
	1 – 5 %	0.2
	< 1 %	0.1
Duration of activity*	< 8h	1
	< 4h	0.6
	< 1h	0.2
	< 15min	0.1
General ventilation**	basic (1 - 3 ACH)	1
	good (3 - 5 ACH)	0.7
	enhanced (5 - 10 ACH)	0.3
Local Exhaust Ventilation**	no	1
	yes	0.1 - 0.05
Dermal protection***	no gloves	1
	chemically resistant gloves according to EN 374 (APF 5)	0.2
	chemically resistant gloves according to EN 374 with basic activity training (APF 10)	0.1
	chemically resistant gloves according to EN 374 with specific activity training (APF 20)	0.05

Input parameter	Specific OC / RMM	Exposure modifying factor
Respiratory protection*	no respirator	1
	respirator with APF 10	0.1
	respirator with APF 20	0.05
Place of use	indoor	1
	outdoor	0.7

* relevant only for inhalation exposure

** relevant only for inhalation exposure and only applicable for indoor use

*** relevant only for dermal exposure

B.9.1 TIER 1 assessment – Modelling calculations

B.9.1.1 Exposure modelling

B9.1.1.1 Manufacturing

Exposure Scenario 1: Manufacture of substance

Description

DMF is produced either via catalysed reaction of dimethylamine and carbon monoxide in methanol or via the reaction of methyl formate with dimethylamine. It may also be prepared on a laboratory scale by reacting dimethylamine with formic acid.

Within the EU, DMF is manufactured within high integrity contained systems were little potential for exposure exists (PROC 1), according to ECHA. Occasional controlled exposure is only expected during sampling (PROC 2) for quality analysis purposes (PROC 15) and during transfer operations (PROC 8b). However, bulk loading is undertaken outdoors under containment (semi-closed process). In case of increased process temperatures for transfer processes, respiratory protection equipment is additionally used to ensure adequate control of exposure.

Table B66. Details on Exposure Scenario 1 (Manufacture of substance) , use conditions and calculated exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	PROC 1; Manufacture (condition 1: indoor, process temp. ≤ 140 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.122	-	-	0.03	0.007	0.011
2	PROC 1; Manufacture (condition 2: outdoor, process temp. ≤ 150 °C)	No, outdoor	No, outdoor	8	100	Apf5 (80 %)	No	0.085	-	-	0.021	0.007	0.010
3	PROC 2; Manufacture (condition 1: outdoor, process temp. ≤ 150 °C)	No, outdoor	No, outdoor	4	100	Apf20 (95 %)	Apf10 (90 %)	21.32	-	-	3.198	0.041	0.498
4	PROC 2; Manufacture (condition 2: outdoor, process temp. ≤ 40 °C)	No, outdoor	No, outdoor	4	100	Apf20 (95 %)	No	8.528	-	-	1.279	0.068	0.251
5	PROC 8b; Manufacture (condition 1: outdoor, process temp. ≤ 40 °C)	No, outdoor	No, outdoor	1	100	Apf20 (95 %)	Apf10 (90 %)	4.264	-	-	0.213	0.686	0.716
6	PROC 8b; Manufacture (condition 2: outdoor, process temp. ≤ 40 °C)	No, outdoor	No, outdoor	4	5-25	Apf20 (95 %)	No	25.58	-	-	3.837	0.411	0.959
7	PROC 15; Manufacture (indoor, process temp. ≤ 40 °C)	Basic	Yes (90 %)	8	100	Apf5 (80 %)	No	6.091	-	-	1.523	0.068	0.286

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden,
Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

B9.1.1.2 Uses by workers in industrial settings

Exposure scenario 2: Formulation of substance

Description

Formulation of the substance takes mainly place in closed systems (PROC 1, PROC 2 and PROC 3) or semi-closed systems (PROC 4). In case of open processes for mixing and blending in batch processes (PROC 5), respiratory protection equipment is used to guarantee operational safety. General transfer processes from/to vessels/large containers at dedicated (PROC 8b) and non-dedicated (PROC 8a) facilities take place indoors with extract ventilation. This also applies for drum and small package filling including weighing (PROC 9). For laboratory activities (PROC 15) involving increased application temperatures, respiratory protection equipment is mandatory.

Table B67. Details on Exposure Scenario 2 (Formulation of substance), use conditions and calculated exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	PROC 1; Formulation (indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.122	-	-	0.03	0.007	0.011
2	PROC 2; Formulation (indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf20 (95 %)	No	12.18	-	-	3.046	0.068	0.503
3	PROC 3; Formulation (indoor, process temp. ≤ 50 °C)	Basic	No	8	100	Apf20 (95 %)	Apf20 (95 %)	6.091	-	-	1.523	0.034	0.252
4	PROC 4; Formulation (indoor, process temp. ≤ 40 °C)	Basic	Yes (90 %)	4	100	Apf20 (95 %)	No	6.091	-	-	0.914	0.343	0.474
5	PROC 5; Formulation (indoor, process temp. ≤ 50 °C)	Basic	Yes (90 %)	8	5-25	Apf20 (95 %)	Apf10 (90 %)	3.655	-	-	0.914	0.411	0.542
6	PROC 8a; Formulation (indoor, process temp. ≤ 40 °C)	Basic	Yes (90 %)	8	5-25	Apf20 (95 %)	No	7.309	-	-	3.046	0.411	0.846
7	PROC 8b; Formulation (indoor, process temp. ≤ 40 °C)	Basic	Yes (95 %)	8	5-25	Apf20 (95 %)	No	1.827	-	-	0.457	0.411	0.476
8	PROC 9; Formulation (indoor, process temp. ≤ 40 °C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	No	6.091	-	-	1.523	0.05	0.268

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
9	PROC 15; Formulation (indoor, process temp. ≤ 60 °C)	Basic	No	8	100	Apf20 (95 %)	Apf20 (95 %)	6.091	-	-	1.523	0.005	0.223

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden
Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

Exposure Scenario 3: Industrial use for the production of fine chemicals

Description

Referring to information from industry, one main use of DMF is as a solvent in chemical synthesis of pharmaceuticals or agrochemicals. Thus, Exposure Scenario 3 refers to the DMF usage for the production of fine chemicals which described the synthesis of chemicals such as Active Pharmaceutical Ingredients (API) and crop protection ingredients.

Although Exposure Scenario 4 refers specifically to the usage of DMF for pharmaceutical applications, this Scenario covers a broader range of fine chemicals. Manufacture of these fine chemicals is mostly carried out in batch processes with synthesis being followed by separation and purification steps. This is undertaken in closed (PROC 1, PROC 2 and PROC 3) as well as semi-closed (PROC 4) and open systems (PROC 5). In case of open processes which could result in significant contact, extract ventilation and respiratory protection equipment are indicated as compulsive Risk Management Measurements. Batch processes might be carried out under pressure, under vacuum or at elevated temperatures. Bulk liquids are mainly transferred (PROC 8a, PROC 8b and PROC 9) directly to above – or below ground bulk storage tanks. In general, these liquids are piped into the plant. Process operations typically involve a batch reactor into which different raw materials are discharged by a carrier solvent (i.e. DMF). Spent solvents are usually collected and recovered on-site. For particular fine chemical preparations, additional processes involving tableting, compression, extrusion and pelletisation (PROC 14) might take place. Resulting exposure is predominately related to volatiles so that respiratory protective device is compulsory for these processes. During substance synthesis, sampling and analytical verification (PROC 15) of the fine chemicals and the solvent itself is expected at different production steps.

Table B68. Details on Exposure Scenario 3 (Industrial use for the production of fine chemicals), use conditions and calculated exposure (CHESAR software tool, v2.2)

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	PROC 1; Production of fine chemicals (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.122	-	-	0.03	0.002	0.006
2	PROC 1; Production of fine chemicals (Condition 2, indoor, process temp. ≤ 150 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.122	-	-	0.03	0.002	0.006
3	PROC 2; Production of fine chemicals (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf20 (95 %)	No	12.18	-	-	3.046	0.068	0.503
4	PROC 2; Production of fine chemicals (Condition 2, outdoor, process temp. ≤ 170 °C)	No, outdoor	No, outdoor	4	100	Apf20 (95 %)	Apf10 (90 %)	21.32	-	-	5.33	0.068	0.829
5	PROC 3; Production of fine chemicals (Condition 1, indoor, process temp.	Basic	No	8	100	Apf20 (95 %)	Apf10 (90 %)	3.655	-	-	0.914	0.034	0.165

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
	≤ 40 °C)												
6	PROC 3; Production of fine chemicals (Condition 2, indoor, process temp. ≤ 160 °C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	6.091	-	-	1.523	0.034	0.252
7	PROC 4; Production of fine chemicals (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf20 (95 %)	Apf10 (90 %)	6.091	-	-	1.523	0.343	0.561
8	PROC 4; Production of fine chemicals (Condition 2, indoor, process temp. ≤ 50 °C)	Basic	No	0.25	100	Apf20 (95 %)	Apf20 (95 %)	12.18	-	-	0.305	0.034	0.078
9	PROC 4; Production of fine chemicals (Condition 3, indoor, process temp. ≤ 160 °C)	Basic	Yes (90 %)	1	100	Apf20 (95 %)	Apf20 (95 %)	6.091	-	-	0.305	0.069	0.113
10	PROC 5; Production of fine chemicals (indoor, process temp. ≤ 70 °C)	Basic	Yes (90 %)	8	5-25	Apf20 (95 %)	Apf20 (95 %)	3.655	-	-	0.914	0.411	0.542
11	PROC 8a; Production of fine chemicals (Condition 1, indoor,	Basic	No	8	5-25	Apf20 (95 %)	Apf20 (95 %)	3.655	-	-	0.914	0.411	0.542

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
	process temp. ≤ 40 °C)												
12	PROC 8a; Production of fine chemicals (Condition 2, indoor, process temp. ≤ 50 °C)	En-hanced	No	4	100	Apf20 (95 %)	Apf20 (95 %)	9.137	-	-	1.371	0.411	0.607
13	PROC 8b; Production of fine chemicals (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	No	8	5-25	Apf20 (95 %)	Apf20 (95 %)	1.827	-	-	0.457	0.411	0.476
14	PROC 8b; Production of fine chemicals (Condition 2, outdoor, process temp. ≤ 40 °C)	No, outdoor	No, outdoor	1	100	Apf20 (95 %)	Apf10 (90 %)	4.264	-	-	0.213	0.686	0.716
15	PROC 8b; Production of fine chemicals (Condition 3, outdoor, process temp. ≤ 40 °C)	No, outdoor	Yes (70 %)	1	100	Apf20 (95 %)	No	8.528 (modified)	-	-	0.426 (modified)	0.686	0.747
16	PROC 8b; Production of fine chemicals (Condition 4, indoor, process temp. ≤ 40 °C)	Basic	Yes (95 %)	1	100	Apf20 (95 %)	No	3.046	-	-	0.152	0.686	0.708
17	PROC 9; Production of fine chemicals (indoor,	Basic	No	8	100	Apf20 (95 %)	Apf20 (95 %)	3.046	-	-	0.761	0.343	0.452

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
	process temp. ≤ 40 °C)												
18	PROC 14; Production of fine chemicals (indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf20 (95 %)	Apf20 (95 %)	3.046	-	-	0.761	0.172	0.281
19	PROC 15; Production of fine chemicals (Condition 1, indoor, process temp. ≤ 40 °C)	En-hanced	Yes (90 %)	8	100	Apf20 (95 %)	Apf20 (95 %)	0.091	-	-	0.023	0.017	0.020
20	PROC 15; Production of fine chemicals (Condition 2, indoor, process temp. ≤ 155 °C)	En-hanced	Yes (90 %)	1	100	Apf20 (95 %)	No	18.27	-	-	0.914	0.003	0.134
21	PROC 19; Production of fine chemicals (indoor, process temp. ≤ 40 °C)	Basic	Yes (90 %)	4	100	Apf20 (95 %)	No	12.18	-	-	1.827	7.072	7.333

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden
Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

Exposure Scenario 4: Industrial use for the production of pharmaceuticals

Description

Within the pharmaceutical industry and in-vitro diagnostic (IVD) medical devices industry, DMF and similar solvents are used in Lab R&D and in the supply chain of Active Pharmaceutical Ingredients (APIs) and IVD Medical Devices. DMF is mainly used as solvent in syntheses and for crystallizing. Frequently, polar aprotic solvents are important for both solubilization of reactants and required product.

The application of solvents mainly occurs in closed processes (PROC 1, PROC 2 and PROC 3). Infrequently, DMF is used in semi-closed processes (PROC 4) during charging, sampling or discharge of material. Mixing and blending operations can also take place in open processes (PROC 5) which provide the opportunity for significant contact. For semi-closed and open processes (indoor use), occupational health and safety is guaranteed by mechanical extract ventilation. General transfer processes (sampling, loading, filling, dumping, etc.) from/to vessels/large containers at non-dedicated (PROC 8a) facilities take place indoors with extract ventilation and respiratory protection. This also applies for drum and small package filling including weighing (PROC 9). For the transfer of substance or preparation (charging/discharging) from/to vessels /large containers at dedicated facilities (PROC 8b), mechanical extract ventilation (i.e. LEV) is often applied. Exhaust ventilation also need to be implemented for quality control of finished products and R&D activities (PROC 15).

Processes which involve intimate and intentional contact (PROC 19 – Hand mixing) were found to bear a potential risk towards Human Health.

Table B69. Details on Exposure Scenario 4 (Industrial use for the production of pharmaceuticals), use conditions and calculated exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	PROC 1; Production of pharmaceuticals (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.122	-	-	0.03	0.007	0.011
2	PROC 1; Production of pharmaceuticals (Condition 2, indoor, process temp. ≤ 100 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.122	-	-	0.03	0.007	0.011
3	PROC 2; Production of pharmaceuticals (indoor, process temp. ≤ 40 °C)	Good	No	8	100	Apf5 (80 %)	No	8.528	-	-	2.132	0.274	0.579
4	PROC 3; Production of pharmaceuticals (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf20 (95 %)	Apf20 (95 %)	1.827	-	-	0.457	0.034	0.099
5	PROC 3; Production of pharmaceuticals (Condition 2, indoor, process temp. ≤ 50 °C)	Basic	No	8	100	Apf20 (95 %)	Apf20 (95 %)	6.091	-	-	1.523	0.034	0.252
6	PROC 3; Production of pharmaceuticals (Condition 3, indoor,	Basic	Yes (90 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	6.091	-	-	1.523	0.034	0.252

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
	process temp. ≤ 120 °C)												
7	PROC 3; Production of pharmaceuticals (Condition 4, indoor, process temp. ≤ 100 °C)	En-hanced	No	8	100	Apf20 (95 %)	Apf20 (95 %)	9.137	-	-	2.284	0.034	0.360
8	PROC 3; Production of pharmaceuticals (Condition 5, outdoor, process temp. ≤ 40 °C)	No, outdoor	No, outdoor	8	100	Apf20 (95 %)	Apf20 (95 %)	1.279	-	-	0.32	0.034	0.080
9	PROC 4; Production of pharmaceuticals (indoor, process temp. ≤ 40 °C)	En-hanced	Yes (90 %)	8	100	Apf10 (90 %)	Apf20 (95 %)	0.091	-	-	0.023	0.686	0.689
10	PROC 5; Production of pharmaceuticals (indoor, process temp. ≤ 100 °C)	Basic	Yes (90 %)	4	>25	Apf20 (95 %)	Fume extraction hood Apf50 (98 %)	6.10 (modified)	-	-	0.91 (modified)	0.411	0.541
11	PROC 8a; Production of pharmaceuticals (Condition 1, indoor, process temp. ≤ 40 °C)	Good	Yes (90 %)	8	100	Apf20 (95 %)	Apf20 (95 %)	0.426	-	-	0.107	0.686	0.701
12	PROC 8a; Production of pharmaceuticals (Condition 2, indoor,	Basic	Yes (90 %)	8	5-25	Apf20 (95 %)	Apf20 (95 %)	9.137	-	-	2.284	0.411	0.737

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
	process temp. ≤ 160 °C)												
13	PROC 8b; Production of pharmaceuticals (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	Yes (95 %)	4	100	Apf20 (95 %)	No	3.046	-	-	0.457	0.686	0.751
14	PROC 8b; Production of pharmaceuticals (Condition 2, indoor, process temp. ≤ 40 °C)	Basic	Yes (95 %)	4	100	Apf20 (95 %)	Apf20 (95 %)	0.152	-	-	0.023	0.686	0.689
15	PROC 8b; Production of pharmaceuticals (Condition 3, indoor, process temp. ≤ 40 °C)	En-hanced	Yes (95 %)	4	5-25	Apf20 (95 %)	No	0.548	-	-	0.082	0.411	0.423
16	PROC 8b; Production of pharmaceuticals (Condition 4, indoor, process temp. ≤ 40 °C)	En-hanced	No	4	1-5	Apf5 (80 %)	No	3.655	-	-	0.548	0.548	0.626
17	PROC 9; Production of pharmaceuticals (indoor, process temp. ≤ 40 °C)	Basic	Yes (90 %)	4	100	Apf20 (95 %)	Apf20 (95 %)	0.305	-	-	0.046	0.343	0.350
18	PROC 15; Production of pharmaceuticals (indoor, process temp. ≤ 40 °C)	Basic	Yes (90 %)	8	100	Apf5 (80 %)	No	6.091	-	-	1.523	0.068	0.286
19	PROC 19; Production	Basic	Yes	4	100	Apf20	Apf10	1.218	-	-	0.183	7.072	7.098

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
	of pharmaceuticals (indoor, process temp. ≤ 40 °C)		(90 %)			(95 %)	(90 %)						

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden
Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

Exposure Scenario 5: Industrial use for the production of polymers

Description

Solvents are used in many different processes within the polymer manufacturing industry (i.e. for dry and wet spinning techniques). The application of solvents occurs in closed processes (PROC 1, PROC 2 and PROC 3) and also in semi-closed processes (PROC 4) during charging, sampling or discharge of material at different process temperatures. To ensure occupational safety, semi-closed processes are associated at least with exhaust ventilation (for indoor use) or with respiratory protection (for outdoor use).

Rarely, mixing and blending operations take place in open processes (PROC 5) which provides the opportunity for significant contact. Here, occupational health and safety is guaranteed by application of respiratory protection equipment. General transfer processes (sampling, loading, filling, dumping, etc.) from/to vessels/large containers at non-dedicated (PROC 8a) facilities take place indoors with extract ventilation and respiratory protection. This also applies for the transfer of substance or preparation (charging/discharging) from/to vessels /large containers at dedicated facilities (PROC 8b) and for drum and small package filling including weighing (PROC 9).

Quality control of finished products and R&D activities (PROC 15) are undertaken under strict RMMs involving extract ventilation and respiratory protection as well.

Processes which involve significant contact (PROC 10 – Roller application or brushing) were found to bear a potential risk towards Human Health.

Table B70. Details on Exposure Scenario 5 (Industrial use for the production of polymers), use conditions and calculated exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	PROC 1; Production of polymers (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.122	-	-	0.03	0.007	0.011
2	PROC 1; Production of polymers (Condition 2, indoor, process temp. ≤ 100 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.122	-	-	0.03	0.007	0.011
3	PROC 2; Production of polymers (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	Yes (90 %)	8	>25	Apf20 (95 %)	Apf10 (90 %)	0.122	-	-	0.03	0.068	0.072
4	PROC 2; Production of polymers (Condition 2, indoor, process temp. ≤ 40 °C)	Basic	Yes (90 %)	8	>25	Apf5 (80 %)	No	1.218	-	-	0.305	0.274	0.318
5	PROC 2; Production of polymers (Condition 3, indoor, process temp. ≤ 90 °C)	En-hanced	Yes (90 %)	8	5-25	Apf5 (80 %)	No	5.482	-	-	1.371	0.164	0.360
6	PROC 3; Production of polymers (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf20 (95 %)	Apf10 (90 %)	3.655	-	-	0.914	0.034	0.165

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
7	PROC 3; Production of polymers (Condition 2, indoor, process temp. ≤ 80 °C)	Basic	Yes (90 %)	8	100	Apf10 (90 %)	Apf20 (95 %)	3.046	-	-	0.761	0.069	0.178
8	PROC 3; Production of polymers (Condition 3, indoor, process temp. ≤ 70 °C)	En-hanced	Yes (90 %)	8	>25	Apf5 (80 %)	No	3.655	-	-	0.914	0.138	0.269
9	PROC 3; Production of polymers (Condition 4, indoor, process temp. ≤ 70 °C)	Good	Yes (90 %)	8	100	Apf5 (80 %)	Apf10 (90 %)	8.528	-	-	2.132	0.138	0.443
10	PROC 4; Production of polymers (Condition 1, indoor, process temp. ≤ 140 °C)	En-hanced	Yes (90 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	3.655	-	-	0.914	0.343	0.474
11	PROC 4; Production of polymers (Condition 2, indoor, process temp. ≤ 55 °C)	Basic	Yes (90 %)	8	>25	Apf20 (95 %)	Apf20 (95 %)	1.218	-	-	0.305	0.343	0.387
12	PROC 4; Production of polymers (Condition 3, indoor, process temp. ≤ 50 °C)	Basic	Yes (90 %)	8	<1	Apf5 (80 %)	No	2.436	-	-	0.609	0.137	0.224
13	PROC 4; Production of polymers (Condition 4, outdoor, process temp. ≤ 40 °C)	No, outdoor	No, outdoor	4	>25	Apf10 (90 %)	Apf20 (95 %)	2.132	-	-	0.32	0.686	0.732

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
14	PROC 4; Production of polymers (Condition 5, indoor, process temp. ≤ 40 °C)	Basic	Yes (90 %)	8	5-25	Apf10 (90 %)	No	3.655	-	-	0.914	0.412	0.543
15	PROC 4; Production of polymers (Condition 6, outdoor, process temp. ≤ 40 °C)	En-hanced	Yes (90 %)	8	100	Apf10 (95 %)	Apf10 (90 %)	0.183	-	-	0.046	0.686	0.693
16	PROC 5; Production of polymers (indoor, process temp. ≤ 40 °C)	Basic	No	8	5-25	Apf20 (95 %)	Apf20 (95 %)	1.827	-	-	0.457	0.411	0.476
17	PROC 8a; Production of polymers (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	1.218	-	-	0.305	0.686	0.730
18	PROC 8a; Production of polymers (Condition 2, indoor, process temp. ≤ 80 °C)	Good	Yes (90 %)	1	100	Apf10 (90 %)	Apf10 (90 %)	21.32	-	-	1.066	0.274	0.426
19	PROC 8b; Production of polymers (indoor, process temp. ≤ 40 °C)	Basic	Yes (95 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	0.305	-	-	0.076	0.686	0.697
20	PROC 9; Production of polymers (indoor, process temp. ≤ 60 °C)	Basic	Yes (90 %)	4	>25	Apf10 (90 %)	Apf10 (90 %)	4.264	-	-	0.64	0.412	0.503
21	PROC 10; Production of polymers (indoor, process temp. ≤ 130	Basic	Yes (90 %)	4	>25	Apf20 (95 %)	Apf10 (90 %)	30.46	-	-	4.568	0.823	1.476

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
	°C)												
22	PROC 15; Production of polymers (indoor, process temp. ≤ 40 °C)	Basic	Yes (90 %)	8	100	Apf5 (80 %)	Apf10 (90 %)	0.609	-	-	0.152	0.068	0.090

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden
Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

Exposure Scenario 6: Industrial use for the production of textiles, leather and fur

Description

DMF is widely used as solvent in the production of polyurethane coated textiles such as artificial leather, rain and protection wear, footwear, medical mattress covers and surgical incise films. In general, hide and skin storage and beamhouse operations are followed by tanyard operations, post-tanning operations and finishing operations. These operations mainly take place in closed processes (PROC 1, PROC 2 and PROC 3). Semi-closed (PROC 4) and/or open processes (PROC 5) are performed under strict RMMs (exhaust ventilation, respiratory protection). These RMMs also apply for general transfer processes (sampling, loading, filling, dumping, etc.) from/to vessels/large containers at dedicated (PROC 8b) facilities and for drum and small package filling including weighing (PROC 9).

Table B71. Details on Exposure Scenario 6 (Industrial use for the production of textiles, leather and fur), use conditions and calculated exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	PROC 1; Production of textiles, leather and fur (indoor, process temp. ≤ 100 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.122	-	-	0.03	0.007	0.011
2	PROC 2; Production of textiles, leather and fur (indoor, process temp. ≤ 70 °C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	No	6.091	-	-	1.523	0.068	0.286
3	PROC 3; Production of textiles, leather and fur (indoor, process temp. ≤ 100 °C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	6.091	-	-	1.523	0.034	0.252
4	PROC 4; Production of textiles, leather and fur (indoor, process temp. ≤ 40 °C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	0.609	-	-	0.152	0.343	0.365
5	PROC 5; Production of textiles, leather and fur (indoor, process temp. ≤ 40 °C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	0.609	-	-	0.152	0.686	0.708
6	PROC 8b; Production of textiles, leather and fur (indoor, process temp.	Basic	Yes (95 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	0.305	-	-	0.076	0.686	0.697

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
	≤ 40 °C)												
7	PROC 9; Production of textiles, leather and fur (indoor, process temp. ≤ 70 °C)	Basic	Yes (90 %)	4	100	Apf20 (95 %)	Apf10 (90 %)	6.091	-	-	0.914	0.206	0.337

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden
Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

Exposure Scenario 7: Industrial use for the manufacture of non-metallic mineral products

Description

This Exposure Scenario describes the usage of DMF for the manufacture of non-metallic products. One specific application is the usage for coating processes. Storage and formulation of DMF is only performed in closed systems (PROC 1, PROC 2 and PROC 3) where only slight opportunity for contact occurs (e.g. through sampling). In this case, industrial spraying (PROC 7) is performed as automated and closed process under strict operational conditions (i.e. operators control room is enclosed and separated from this process).

Table B72. Details on Exposure Scenario 7 (Industrial use for the manufacture of non-metallic mineral products), use conditions and calculated exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	PROC 1; Manufacture of non-metallic minerals (indoor, process temp. ≤ 45 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.122	-	-	0.03	0.007	0.011
2	PROC 2; Manufacture of non-metallic minerals (indoor, process temp. ≤ 45 °C)	Basic	No	0.25	100	Apf20 (95 %)	Apf20 (95 %)	3.046	-	-	0.076	0.007	0.018
3	PROC 3; Manufacture of non-metallic minerals (indoor, process temp. ≤ 45 °C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	Apf20 (95 %)	0.609	-	-	0.152	0.034	0.056
4	PROC 7; Manufacture of non-metallic minerals (indoor, process temp. ≤ 250 °C)	Basic	Yes (95 %)	4	>25	Apf20 (95 %)	No	Automated process	-	-	Automated process	Automated process	-

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden
Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

Exposure Scenario 8: Industrial use for the manufacture of perfumes / fragrances

Description

This Exposure Scenario refers to the production of perfumes/fragrances. Relevant operations are only carried out in closed batch processes (PROC 3) with synthesis being followed by separation and purification steps. Transfer processes of substances or preparations (sampling, loading, filling, dumping, etc.) are merely performed from/to vessels/large containers at dedicated facilities (PROC 8b).

Table B73. Details on Exposure Scenario 8 (Industrial use for the manufacture of perfumes / fragrances), use conditions and calculated exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	PROC 3; Manufacture of perfumes / fragrances (indoor, process temp. ≤ 50 °C)	Basic	No	4	5-25	Apf20 (95 %)	Apf20 (95 %)	3.655	-	-	0.548	0.012	0.090
2	PROC 8b; Manufacture of perfumes / fragrances (indoor, process temp. ≤ 40 °C)	Basic	No	4	100	Apf20 (95 %)	Apf20 (95 %)	3.046	-	-	0.457	0.686	0.751

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden
Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

B9.1.1.3 Uses by professional workers

Exposure Scenario 9: Professional use as laboratory agent

Description

The substance DMF is exclusively used in industrial settings, except for the use as laboratory chemical (which is the only use registered for professional workers). Strict occupational controls and chemical hygiene procedures are applied, since the handling of hazardous chemicals is day-to-day routine for this profession.

Handling of the substance can be described by intensive laboratory activities (PROC 15) at small scale laboratories. General transfer processes (charging/discharging) are undertaken from/to vessels/large containers at non-dedicated facilities (PROC 8a).

Table B74. Details on Exposure Scenario 9 (Professional use as laboratory agent), use conditions and calculated exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Ventilation		Duration	Concen-tration	Gloves	RPE*	Exposure (acute; systemic)			Exposure (long-term; systemic)		
		General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	PROC 8a; Professional use as laboratory agent (indoor, process temp. ≤ 40 °C)	Good	Yes (80 %)	4	5-25	Apf20 (95 %)	Apf10 (90 %)	2.558	-	-	0.384	0.411	0.466
2	PROC 15; Professional use as laboratory agent (indoor, process temp. ≤ 40 °C)	Basic	Yes (80 %)	8	100	Apf10 (90 %)	No	12.18	-	-	3.046	0.034	0.469

*: RPE = Respiratory Protection Equipment

**: worst case internal body burden

Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

B.9.1.1.4 Uses by consumer products

Consumer use is not intended for DMF.

B.9.1.2 Risk characterisation

B.9.1.2.1 RCRs – industrial uses

Exposure Scenario 1: Manufacture of substance

Table B75. Results of Risk Characterisation for Exposure Scenario 1 (Manufacture of substance): Risk Characterisation Ratios (RCRs) for acute and long-term systemic worker exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Risk Characterisation (acute; systemic)			Risk Characterisation (long-term; systemic)		
		RCR Inhalative	RCR Dermal	RCR Combined *	RCR Inhalative	RCR Dermal	RCR Combined *
1	PROC 1; Manufacture (condition 1: indoor, process temp. ≤ 140 °C)	<0.01	-	-	<0.01	<0.01	0.011
2	PROC 1; Manufacture (condition 2: outdoor, process temp. ≤ 150 °C)	<0.01	-	-	<0.01	<0.01	0.01
3	PROC 2; Manufacture (condition 1: outdoor, process temp. ≤ 150 °C)	0.711	-	-	0.213	0.052	0.265
4	PROC 2; Manufacture (condition 2: outdoor, process temp. ≤ 40 °C)	0.284	-	-	0.085	0.087	0.172
5	PROC 8b; Manufacture (condition 1: outdoor, process temp. ≤ 40 °C)	0.142	-	-	0.014	0.868	0.882
6	PROC 8b; Manufacture (condition 2: outdoor, process temp. ≤ 40 °C)	0.853	-	-	0.256	0.521	0.777
7	PROC 15; Manufacture (indoor, process temp. ≤ 40 °C)	0.203	-	-	0.102	0.086	0.188

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden

Exposure scenario 2: Formulation of substance

Table B76. Results of Risk Characterisation for Exposure Scenario 2 (Formulation of substance): Risk Characterisation Ratios (RCRs) for acute and long-term systemic worker exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Risk Characterisation (acute; systemic)			Risk Characterisation (long-term; systemic)		
		RCR Inhalative	RCR Dermal	RCR Combined	RCR Inhalative	RCR Dermal	RCR Combined
1	PROC 1; Formulation (indoor, process temp.≤ 40 °C)	<0.01	-	-	<0.01	<0.01	0.011
2	PROC 2; Formulation (indoor, process temp. ≤ 40 °C)	0.406	-	-	0.203	0.087	0.290
3	PROC 3; Formulation (indoor, process temp. ≤ 50 °C)	0.203	-	-	0.102	0.044	0.145
4	PROC 4; Formulation (indoor, process temp. ≤ 40 °C)	0.203	-	-	0.061	0.434	0.495
5	PROC 5; Formulation (indoor, process temp. ≤ 50 °C)	0.122	-	-	0.061	0.521	0.582
6	PROC 8a; Formulation (indoor, process temp. ≤ 40 °C)	0.244	-	-	0.122	0.521	0.643
7	PROC 8b; Formulation (indoor, process temp. ≤ 40 °C)	0.061	-	-	0.030	0.521	0.551
8	PROC 9; Formulation (indoor, process temp. ≤ 40 °C)	0.203	-	-	0.102	0.434	0.536
9	PROC 15; Formulation (indoor, process temp. ≤ 60 °C)	0.203	-	-	0.102	0.022	0.123

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden

Exposure Scenario 3: Industrial use for the production of fine chemicals

Table B77. Results of Risk Characterisation for Exposure Scenario 3 (Industrial use for the production of fine chemicals): Risk Characterisation Ratios (RCRs) for acute and long-term systemic worker exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Risk Characterisation (acute; systemic)			Risk Characterisation (long-term; systemic)		
		RCR Inhalative	RCR Dermal	RCR Combined	RCR Inhalative	RCR Dermal	RCR Combined
1	PROC 1; Production of fine chemicals (Condition 1, indoor, process temp. ≤ 40 °C)	<0.01	-	-	<0.01	<0.01	0.011
2	PROC 1; Production of fine chemicals (Condition 2, indoor, process temp. ≤ 150 °C)	<0.01	-	-	<0.01	<0.01	0.011
3	PROC 2; Production of fine chemicals (Condition 1, indoor, process temp. ≤ 40 °C)	0.406	-	-	0.203	0.087	0.290
4	PROC 2; Production of fine chemicals (Condition 2, outdoor, process temp. ≤ 170 °C)	0.711	-	-	0.355	0.087	0.442
5	PROC 3; Production of fine chemicals (Condition 1, indoor, process temp. ≤ 40 °C)	0.122	-	-	0.061	0.044	0.105
6	PROC 3; Production of fine chemicals (Condition 2, indoor, process temp. ≤ 160 °C)	0.203	-	-	0.102	0.044	0.145
7	PROC 4; Production of fine chemicals (Condition 1, indoor, process temp. ≤ 40 °C)	0.203	-	-	0.102	0.434	0.536
8	PROC 4; Production of fine chemicals (Condition 2, indoor, process temp. ≤ 50 °C)	0.406	-	-	0.02	0.043	0.064
9	PROC 4; Production of fine chemicals (Condition 3, indoor, process temp. ≤ 160 °C)	0.203	-	-	0.02	0.087	0.107
10	PROC 5; Production of fine chemicals (indoor, process temp. ≤ 70 °C)	0.122	-	-	0.061	0.521	0.582
11	PROC 8a; Production of fine	0.122	-	-	0.061	0.521	0.582

CS No.	Process Category (PROC)	Risk Characterisation (acute; systemic)			Risk Characterisation (long-term; systemic)		
		RCR Inhalative	RCR Dermal	RCR Combined	RCR Inhalative	RCR Dermal	RCR Combined
	chemicals (Condition 1, indoor, process temp. ≤ 40 °C)						
12	PROC 8a; Production of fine chemicals (Condition 2, indoor, process temp. ≤ 50 °C)	0.305	-	-	0.091	0.582	0.612
13	PROC 8b; Production of fine chemicals (Condition 1, indoor, process temp. ≤ 40 °C)	0.061	-	-	0.03	0.521	0.551
14	PROC 8b; Production of fine chemicals (Condition 2, outdoor, process temp. ≤ 40 °C)	0.142	-	-	0.014	0.868	0.882
15	PROC 8b; Production of fine chemicals (Condition 3, outdoor, process temp. ≤ 40 °C)	0.284	-	-	0.028	0.868	0.896
16	PROC 8b; Production of fine chemicals (Condition 4, indoor, process temp. ≤ 40 °C)	0.102	-	-	0.01	0.868	0.878
17	PROC 9; Production of fine chemicals (indoor, process temp. ≤ 40 °C)	0.102	-	-	0.051	0.434	0.485
18	PROC 14; Production of fine chemicals (indoor, process temp. ≤ 40 °C)	0.102	-	-	0.051	0.217	0.268
19	PROC 15; Production of fine chemicals (Condition 1, indoor, process temp. ≤ 40 °C)	<0.01	-	-	<0.01	0.022	0.023
20	PROC 15; Production of fine chemicals (Condition 2, indoor, process temp. ≤ 155 °C)	0.609	-	-	0.061	<0.01	0.065
21	PROC 19; Production of fine chemicals (indoor, process temp. ≤ 40 °C)	0.406	-	-	0.122	8.951	9.073

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden

Exposure Scenario 4: Industrial use for the production of pharmaceuticals

Table B78. Results of Risk Characterisation for Exposure Scenario 4 (Industrial use for the production of pharmaceuticals): Risk Characterisation Ratios (RCRs) for acute and long-term systemic worker exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Risk Characterisation (acute; systemic)			Risk Characterisation (long-term; systemic)		
		RCR Inhalative	RCR Dermal	RCR Combined	RCR Inhalative	RCR Dermal	RCR Combined
1	PROC 1; Production of pharmaceuticals (Condition 1, indoor, process temp. ≤ 40 °C)	<0.01	-	-	<0.01	<0.01	0.011
2	PROC 1; Production of pharmaceuticals (Condition 2, indoor, process temp. ≤ 100 °C)	<0.01	-	-	<0.01	<0.01	0.011
3	PROC 2; Production of pharmaceuticals (indoor, process temp. ≤ 40 °C)	0.284	-	-	0.142	0.347	0.489
4	PROC 3; Production of pharmaceuticals (Condition 1, indoor, process temp. ≤ 40 °C)	0.061	-	-	0.03	0.044	0.074
5	PROC 3; Production of pharmaceuticals (Condition 2, indoor, process temp. ≤ 50 °C)	0.203	-	-	0.102	0.044	0.145
6	PROC 3; Production of pharmaceuticals (Condition 3, indoor, process temp. ≤ 120 °C)	0.203	-	-	0.102	0.044	0.145
7	PROC 3; Production of pharmaceuticals (Condition 4, indoor, process temp. ≤ 100 °C)	0.305	-	-	0.152	0.044	0.196
8	PROC 3; Production of pharmaceuticals (Condition 5, outdoor, process temp. ≤ 40 °C)	0.043	-	-	0.021	0.044	0.065
9	PROC 4; Production of pharmaceuticals (indoor, process temp. ≤ 40 °C)	<0.01	-	-	<0.01	0.868	0.870
10	PROC 5; Production of pharmaceuticals (indoor, process temp. ≤ 100 °C)	0.203	-	-	0.060	0.521	0581
11	PROC 8a; Production of pharmaceuticals (Condition 1, indoor, process temp. ≤ 40 °C)	0.014	-	-	<0.01	0.868	0.875

CS No.	Process Category (PROC)	Risk Characterisation (acute; systemic)			Risk Characterisation (long-term; systemic)		
		RCR Inhalative	RCR Dermal	RCR Combined	RCR Inhalative	RCR Dermal	RCR Combined
12	PROC 8a; Production of pharmaceuticals (Condition 2, indoor, process temp. ≤ 160 °C)	0.305	-	-	0.152	0.521	0.673
13	PROC 8b; Production of pharmaceuticals (Condition 1, indoor, process temp. ≤ 40 °C)	0.102	-	-	0.03	0.868	0.898
14	PROC 8b; Production of pharmaceuticals (Condition 2, indoor, process temp. ≤ 40 °C)	<0.01	-	-	<0.01	0.868	0.869
15	PROC 8b; Production of pharmaceuticals (Condition 3, indoor, process temp. ≤ 40 °C)	0.018	-	-	<0.01	0.521	0.526
16	PROC 8b; Production of pharmaceuticals (Condition 4, indoor, process temp. ≤ 40 °C)	0.122	-	-	0.037	0.694	0.731
17	PROC 9; Production of pharmaceuticals (indoor, process temp. ≤ 40 °C)	0.01	-	-	<0.01	0.434	0.437
18	PROC 15; Production of pharmaceuticals (indoor, process temp. ≤ 40 °C)	0.203	-	-	0.102	0.086	0.188
19	PROC 19; Production of pharmaceuticals (indoor, process temp. ≤ 40 °C)	0.041	-	-	0.012	8.951	8.963

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden

Exposure Scenario 5: Industrial use for the production of polymers

Table B79. Results of Risk Characterisation for Exposure Scenario 5 (Industrial use for the production of polymers): Risk Characterisation Ratios (RCRs) for acute and long-term systemic worker exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Risk Characterisation (acute; systemic)			Risk Characterisation (long-term; systemic)		
		RCR Inhalative	RCR Dermal	RCR Combined	RCR Inhalative	RCR Dermal	RCR Combined
1	PROC 1; Production of polymers (Condition 1, indoor, process temp. ≤ 40 °C)	<0.01	-	-	<0.01	<0.01	0.011
2	PROC 1; Production of polymers (Condition 2, indoor, process temp. ≤ 100 °C)	<0.01	-	-	<0.01	<0.01	0.011
3	PROC 2; Production of polymers (Condition 1, indoor, process temp. ≤ 40 °C)	<0.01	-	-	<0.01	0.087	0.089
4	PROC 2; Production of polymers (Condition 2, indoor, process temp. ≤ 40 °C)	0.041	-	-	0.02	0.347	0.367
5	PROC 2; Production of polymers (Condition 3, indoor, process temp. ≤ 90 °C)	0.183	-	-	0.091	0.208	0.300
6	PROC 3; Production of polymers (Condition 1, indoor, process temp. ≤ 40 °C)	0.122	-	-	0.061	0.044	0.105
7	PROC 3; Production of polymers (Condition 2, indoor, process temp. ≤ 80 °C)	0.102	-	-	0.051	0.087	0.138
8	PROC 3; Production of polymers (Condition 3, indoor, process temp. ≤ 70 °C)	0.122	-	-	0.061	0.175	0.236
9	PROC 3; Production of polymers (Condition 4, indoor, process temp. ≤ 70 °C)	0.284	-	-	0.142	0.175	0.317
10	PROC 4; Production of polymers (Condition 1, indoor, process temp. ≤ 140 °C)	0.122	-	-	0.061	0.434	0.495
11	PROC 4; Production of	0.041	-	-	0.02	0.434	0.454

CS No.	Process Category (PROC)	Risk Characterisation (acute; systemic)			Risk Characterisation (long-term; systemic)		
		RCR Inhalative	RCR Dermal	RCR Combined	RCR Inhalative	RCR Dermal	RCR Combined
	polymers (Condition 2, indoor, process temp. ≤ 55 °C)						
12	PROC 4; Production of polymers (Condition 3, indoor, process temp. ≤ 50 °C)	0.081	-	-	0.041	0.174	0.214
13	PROC 4; Production of polymers (Condition 4, outdoor, process temp. ≤ 40 °C)	0.071	-	-	0.021	0.868	0.890
14	PROC 4; Production of polymers (Condition 5, indoor, process temp. ≤ 40 °C)	0.122	-	-	0.061	0.521	0.582
15	PROC 4; Production of polymers (Condition 6, outdoor, process temp. ≤ 40 °C)	<0.01	-	-	<0.01	0.868	0.871
16	PROC 5; Production of polymers (indoor, process temp. ≤ 40 °C)	0.061	-	-	0.030	0.521	0.551
17	PROC 8a; Production of polymers (Condition 1, indoor, process temp. ≤ 40 °C)	0.041	-	-	0.02	0.868	0.888
18	PROC 8a; Production of polymers (Condition 2, indoor, process temp. ≤ 80 °C)	0.711	-	-	0.071	0.347	0.418
19	PROC 8b; Production of polymers (indoor, process temp. ≤ 40 °C)	<0.01	-	-	<0.01	0.868	0.873
20	PROC 9; Production of polymers (indoor, process temp. ≤ 60 °C)	0.142	-	-	0.043	0.521	0.564
21	PROC 10; Production of polymers (indoor, process temp. ≤ 130 °C)	1.015	-	-	0.305	1.042	1.346
22	PROC 15; Production of polymers (indoor, process temp. ≤ 40 °C)	0.02	-	-	0.01	0.086	0.096

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden

Exposure Scenario 6: Industrial use for the production of textiles, leather and fur

Table B80. Results of Risk Characterisation for Exposure Scenario 6 (Industrial use for the production of textiles, leather and fur): Risk Characterisation Ratios (RCRs) for acute and long-term systemic worker exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Risk Characterisation (acute; systemic)			Risk Characterisation (long-term; systemic)		
		RCR Inhalative	RCR Dermal	RCR Combined	RCR Inhalative	RCR Dermal	RCR Combined
1	PROC 1; Production of textiles, leather and fur (indoor, process temp. ≤ 100 °C)	<0.01	-	-	<0.01	<0.01	0.011
2	PROC 2; Production of textiles, leather and fur (indoor, process temp. ≤ 70 °C)	0.203	-	-	0.102	0.087	0.188
3	PROC 3; Production of textiles, leather and fur (indoor, process temp. ≤ 100 °C)	0.203	-	-	0.102	0.044	0.145
4	PROC 4; Production of textiles, leather and fur (indoor, process temp. ≤ 40 °C)	0.02	-	-	0.01	0.434	0.444
5	PROC 5; Production of textiles, leather and fur (indoor, process temp. ≤ 40 °C)	0.02	-	-	0.01	0.868	0.878
6	PROC 8b; Production of textiles, leather and fur (indoor, process temp. ≤ 40 °C)	0.01	-	-	<0.01	0.868	0.873
7	PROC 9; Production of textiles, leather and fur (indoor, process temp. ≤ 70 °C)	0.203	-	-	0.061	0.260	0.321

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden

Exposure Scenario 7: Industrial use for the manufacture of non-metallic mineral products

Table B81. Results of Risk Characterisation for Exposure Scenario 7 (Industrial use for the manufacture of non-metallic mineral products): Risk Characterisation Ratios (RCRs) for acute and long-term systemic worker exposure (CHESAR software tool, v2.2)

CS No.	Process Category (PROC)	Risk Characterisation (acute; systemic)			Risk Characterisation (long-term; systemic)		
		RCR Inhalative	RCR Dermal	RCR Combined	RCR Inhalative	RCR Dermal	RCR Combined
1	PROC 1; Manufacture of non-metallic minerals (indoor, process temp. ≤ 45 °C)	<0.01	-	-	<0.01	<0.01	0.011
2	PROC 2; Manufacture of non-metallic minerals (indoor, process temp. ≤ 45 °C)	0.102	-	-	<0.01	<0.01	0.014
3	PROC 3; Manufacture of non-metallic minerals (indoor, process temp. ≤ 45 °C)	0.02	-	-	0.01	0.044	0.054
4	PROC 7; Manufacture of non-metallic minerals (indoor, process temp. ≤ 250 °C)	Automated process (qualitative assess-ment)	Automated process (qualitative assess-ment)	Automated process (qualitative assess-ment)	Automated process (qualitative assess-ment)	Automated process (qualitative assess-ment)	Automated process (qualitative assess-ment)

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden

Exposure Scenario 8: Industrial use for the manufacture of perfumes / fragrances

Table B82. Results of Risk Characterisation for Exposure Scenario 8 (Industrial use for the manufacture of perfumes / fragrances): Risk Characterisation Ratios (RCRs) for acute and long-term systemic worker exposure (CHESAR software tool, v2.2).

CS No.	Process Category (PROC)	Risk Characterisation (acute; systemic)			Risk Characterisation (long-term; systemic)		
		RCR Inhalative	RCR Dermal	RCR Combined	RCR Inhalative	RCR Dermal	RCR Combined
1	PROC 3; Manufacture of perfumes / fragrances (indoor, process temp. ≤ 50 °C)	0.122	-	-	0.037	0.016	0.052
2	PROC 8b; Manufacture of perfumes / fragrances (indoor, process temp. ≤ 40 °C)	0.102	-	-	0.03	0.868	0.898

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden

B.9.1.2.2 RCRs – professional uses

Exposure Scenario 9: Professional use as laboratory agent

Table B83. Results of Risk Characterisation for Exposure Scenario 9 (Professional use as laboratory agent), Risk Characterisation Ratios (RCRs) for acute and long-term systemic professional exposure (CHESAR software tool, v2.2)

CS No.	Process category (PROC)	Risk Characterisation (acute; systemic)			Risk Characterisation (long-term; systemic)		
		RCR Inhalative	RCR Dermal	RCR Combined	RCR Inhalative	RCR Dermal	RCR Combined
1	PROC 8a; Professional use as laboratory agent (indoor, process temp. ≤ 40 °C)	0.085	-	-	0.026	0.520	0.563
2	PROC 15; Professional use as laboratory agent (indoor, process temp. ≤ 40 °C)	0.406	-	-	0.203	0.043	0.246

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden

B.9.2 TIER 2 assessment – Measured data

Introduction

Due to the fact that relevant measured data from several different industrial sites are available, a TIER 2 assessment was additionally elaborated. Measured data were specifically requested from relevant Downstream Users via the second questionnaire (please refer to section B.9 for further information).

Measured data by BASF were already submitted to ECHA via the document "BASF comments to the Draft background document for N,N-dimethylformamide (DMF), submitted by ECHA on 24 June 2013". In order to show that measured data are well below the Occupational Exposure Limits, the BASF workplace measurements are displayed below (see Table B84). Please refer to Appendix II of the respective CSR (submitted February 2014) for the full version of this document.

Table B84. BASF SE Workplace measurements (from "BASF comments to the Draft background document for N,N-dimethylformamide (DMF)).

Manufacturing process step	Workplace concentration (e.g. mg/m3)	Basis for estimate (how measured or estimated)
Production - PROC 1, 2: Use in closed process, no likelihood of exposure	<0.09 – <0.12 mg/m³ Personnel shift mean value	Routine OEL Measurement of BASF (not detectable in 6 measurement between 2005 and 2010)
Production - PROC 1,2 : Use in closed process, no likelihood of exposure (Distillation)	<0.034 – <0.16 mg/m³ Personnel shift mean value	Routine OEL Measurement of BASF (not detectable in 12 measurement between 2005 and 2010)
Filling - PROC 8b: Transfer of substance or preparation (charging/ discharging) from/to vessels/large Containers at dedicated facilities	<0.28 – <0.64 mg/m³ Personnel shift mean value	Routine OEL Measurement of BASF (not detectable in 9 measurement between 2005 and 2010)
Filling - PROC 8b: Transfer of substance or preparation (charging/ discharging) from/to vessels/large	0,189 mg/m³ Shift mean value Personnel Peak value	Routine OEL Measurement of BASF. (1 single value with detectable DMF – usually DMF is not detectable)
Use as solvent in product synthesis at BASF. Includes PROC 1, 2, 3, 4, 8a, 8b	<0.034 - < 0.59 mg/m³ Personnel shift mean value	Routine OEL Measurement of BASF (not detectable in 10 measurement between 2005 and 2010)
Use for industrial cleaning (Ludwigshafen) Includes PROC 1, 2, 3, 4, 8a, 8b	< 0.11 - < 0.12 mg/m³	Routine OEL Measurement of BASF (not detectable in 3 measurement between 2005 and 2010)
Use for industrial cleaning (Ludwigshafen) Includes PROC 1, 2, 3, 4, 8a, 8b	4.2 -6.9 mg/m³ Personnel shift mean value	Routine OEL Measurement of BASF (detectable in 2 measurement between 2005 and 2010)
Use for industrial cleaning (Antwerp) Includes PROC 1, 2, 3, 4, 8a, 8b	2.7-3.0 mg/m³ Stationary	Routine OEL Measurement of BASF (detectable in 10 measurement between 1998 and 2001)
Use for industrial cleaning (Antwerp) Includes PROC 1, 2, 3, 4, 8a, 8b	< 0.2 mg/m³ Stationary	Routine OEL Measurement of BASF (not detectable in 3 measurement after introduction of new technical measurement in 2001-2011)
Use for industrial cleaning (Antwerp) Includes PROC 1, 2, 3, 4, 8a, 8b	<0.2 mg/m³ Personnel shift mean value	Routine OEL Measurement of BASF (not detectable in 19 measurement between 2001 and 2011)

Additional measured data by several industry sectors were gathered. These data are differentiated by the Identified Uses / Exposure Scenarios in which the information (measured workplace concentration) is correlated to specific processes (PROCs), Risk Management Measures (RMMs) and Operational Conditions (OCs). The Identified Uses are identical to the ones which are described in section B.9.1 of this document. An overview of all gathered (measured) data is provided in the table below.

B.9.2.1 Exposure modelling and risk characterisation

Remark: For the respective RCR calculations, measured workplace concentrations were either compared to the short-term exposure limits (STEL) of 30 mg/m³ (in case of mean value for 15 min) or the time-weighted average (TWA) limit of 15 mg/m³ (in case of mean value for 8 hours). If measured concentrations could not be related to the STEL or TWA, the TWA value was used for the RCR calculation.

Table B85. Overview of all measured data which has been provided by different Downstream Users (submitted to ECHA in February 2014).

ES	Source of data	PROC	Concen-tration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	RCR	Remarks on measured data (as provided by data source)
1	A	8b	100	< 2 h	basic general ventilation	outdoor, ambient temperature	< 0.4 mg/m³	0.027	DMF concentration below analytical limit of quantification (< 0,4 mg/m³)
1	A	8b	20 - 100	< 10 min	basic general ventilation	outdoor, ambient temperature	< 0.4 mg/m³	0.027	DMF concentration below analytical limit of quantification (< 0,4 mg/m³)
1	A	15	20 - 100	< 8 h	enhanced general ventilation, LEV	indoor, ambient	< 0.4 mg/m³	0.027	DMF concentration below analytical limit of quantification (< 0,4 mg/m³)
2	B	3	20 - 80	<1h	basic general ventilation, LEV	indoor, < 50 °C	< 0.5 mg/m³	0.033	no remarks provided
2	B	4	20 - 80	<4h	basic general ventilation, LEV	indoor, < 40 °C	< 0.5 mg/m³	0.033	no remarks provided
2	B	5	20 - 80	<2h	basic general ventilation, LEV	indoor, < 50 °C	< 0.5 mg/m³	0.033	no remarks provided
2	B	9	100	<1h	basic general ventilation, LEV	indoor, ambient	< 0.5 mg/m³	0.033	no remarks provided

ES	Source of data	PROC	Concen-tration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	RCR	Remarks on measured data (as provided by data source)
2	B	15	100	<4h	LEV	indoor, 20 – 60 °C	< 0.5 mg/m³	0.033	no remarks provided
3	C	15	> 25	< 8 h	enhanced general ventilation, LEV	indoor	≤ 3 mg/m³	0.20	no remarks provided
3	C	3	100	< 8 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 0.4 ppm [1.2 mg/m³]	0.08	concentration below the analytical limit of quantification (0.4 ppm for VOC); PID detector has been used; continuous measurements for 1 hour (intervals of 30 seconds)
3	C	4	100	< 8 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 0.4 ppm [1.2 mg/m³]	0.08	concentration below the analytical limit of quantification (0.4 ppm for VOC); PID detector has been used; continuous measurements for 1 hour (intervals of 30 seconds)
3	C	15	100	< 8 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 0.4 ppm [1.2 mg/m³]	0.08	concentration below the analytical limit of quantification (0.4 ppm for VOC); PID detector has been used; continuous measurements for 1 hour (intervals of 30 seconds)
3	D	1	> 25	< 8 h	enhanced general ventilation, LEV	indoor, 50 – 140 °C	0.002 - 1.8 mg/m³	0.12	Measurements were performed 2009, 2011 and 2013. The measurements were taken in the room ventilation system, where air is drawn out at the bottom of the building via big exhaust fans. The flow in the chimney is measured in order to ensure a laminar flow, before the TD-tube (Thermal Desorption) is inserted. The TD-tube is placed in the chimney and a pump is connected to active draw air into the tube. This is done for an hour and three consecutive measurements are taken. A GC-MS apparatus is used to determine the concentration of the substances in the air.

ES	Source of data	PROC	Concen-tration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	RCR	Remarks on measured data (as provided by data source)
									Sampling is done according to DS/EN 13649 "Stationary Source Emissions – Determination of the mass concentration of individual gaseous compounds". [1. Udgave 2001-12-14, Dansk Standard] Analytical method used corresponds to EPA/625/R-96/010b - Compendium of Methods for the Determination of Toxic Organic Compounds in Ambient Air, Second Edition, Compendium Method TO-17, Determination of Volatile Organic Compounds in Ambient Air Using Active Sampling. Deviation from method: 3-bed sorbent tubes are used. Provided by Markes: Metal tube 5240 – Tenax TA/Carbopack X/UniCarb.
4	E	3	100	< 1 min	no RMMs provided	outdoor, ambient temperature	5 ppm [15 mg/m³]	0.50	peak exposure
4	F	8b	100	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 0.1 mg/m³	<0.01	based on limited number of samples
4	G	3	100	< 8 h	basic general ventilation, LEV	indoor, ≤ 100 °C	< OEL	Qual**	The available data are more than 10 years old.

ES	Source of data	PROC	Concen-tration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	RCR	Remarks on measured data (as provided by data source)
4	H	8b	100	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 0.79 ppm [2.37 mg/m³]	0.158	Personal monitoring in operator breathing zone using 3M - 3500 passive badge - Analysis by Gas Chromatography O8(U) UKAS Accredited
4	H	8b	1 - 5	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	0.81 mg/m³	0.054	Personal monitoring in operator breathing zone using 3M - 3500 passive badge - Analysis by Gas Chromatography O8(U) UKAS Accredited (8h TWA)
4	H	8b	< 1	< 15 min	enhanced general ventilation, LEV	indoor, ambient temperature	0.6 ppm [1.8 mg/m³]	0.12	Personal monitoring in operator breathing zone using 3M - 3500 passive badge - Analysis by Gas Chromatography O8(U) UKAS Accredited (8 h TWA)
4	I	8b	100	< 1 h	basic general ventilation, LEV	indoor, ambient temperature	≤ 0.2 mg/m³	<0.01	no remarks provided
4	J	1	> 25	< 8 h	enhanced general ventilation	indoor, 20 – 100 °C	< 0.01 mg/m³	<0.01	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
4	J	1	5 - 25	< 8 h	enhanced general ventilation	indoor, 20 – 100 °C	< 0.01 mg/m³	<0.01	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
4	J	1	1 - 5	< 8 h	enhanced general ventilation	indoor, 20 – 100 °C	< 0.01 mg/m³	<0.01	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
4	J	1	> 25	< 4 h	enhanced general ventilation	indoor, 100 °C	< 15 mg/m³	Qual**	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.

ES	Source of data	PROC	Concen-tration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	RCR	Remarks on measured data (as provided by data source)
4	J	3	> 25	< 8 h	enhanced general ventilation	indoor, 20 – 100 °C	< 0.01 mg/m³	<0.01	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
4	J	3	5 - 25	< 8 h	enhanced general ventilation	indoor, 20 – 100 °C	< 0.01 mg/m³	<0.01	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
4	J	3	1 - 5	< 8 h	enhanced general ventilation	indoor, 20 – 100 °C	< 0.01 mg/m³	<0.01	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
4	J	4	> 25	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 15 mg/m³	Qual**	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
4	J	4	5 - 25	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 15 mg/m³	Qual**	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
4	J	4	1 - 5	< 1 h	enhanced general ventilation	indoor, ambient temperature	< 15 mg/m³	Qual**	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
4	J	8a	> 25	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 15 mg/m³	Qual**	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.

ES	Source of data	PROC	Concen-tration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	RCR	Remarks on measured data (as provided by data source)
4	J	8a	5 - 25	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 15 mg/m³	Qual**	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
4	J	8a	1 - 5	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 15 mg/m³	Qual**	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
4	J	8b	100	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 15 mg/m³	Qual**	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
4	J	9	100	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 15 mg/m³	Qual**	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
4	J	15	100	< 8 h	good general ventilation, LEV	indoor, ambient temperature	< 0.01 mg/m³	<0.01	DMF concentration below analytical limit of quantification (< 0.01 mg/m³);
4	K	2	80 - 100	< 1 h	fume hood, LEV	indoor, ambient temperature	< OEL	Qual**	Occupational hygiene monitoring was performed by using Draeger DMF 183 (QC 30617 exp. 6.2016) tubes for the operations performed such as opening the DMF drum. EH 40 gives DMF 8 hr TWA = 5 ppm and STEL = 10 ppm. No colour change was observed during the monitoring.

ES	Source of data	PROC	Concen-tration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	RCR	Remarks on measured data (as provided by data source)
5	B	3	20 - 80	< 2h	basic general ventilation, LEV	indoor, 30 – 70 °C	< 0.5 mg/m³	0.033	no remarks provided
5	B	4	20 - 80	< 6h	basic general ventilation, LEV	indoor, < 55 °C	< 0.5 mg/m³	0.033	no remarks provided
5	L	8b	100	< 1h	basic general ventilation, LEV	indoor, ambient temperature	0.8 mg/m³	0.053	DE concentration
5	L	1	> 25	< 8h	basic general ventilation, LEV	indoor, 100 °C	0.8 mg/m³	0.053	DE concentration
5	M	9	> 25	< 4 h	good general ventilation, LEV	indoor, 30 – 60 °C	0.2 - 0.5 mg/m³	0.033	Packaging. Last monitoring in 2011.
5	N	3	> 25	< 8 h	enhanced general ventilation	indoor, 55 °C	1.63 mg/m³	0.109	2013 Measure : full shift (8h) - sensor carried by the operator
5	N	4	> 25	< 1 h	enhanced general ventilation, LEV	indoor, 30 °C	9 mg/m³	0.30	2013 Measure : mean value of 15 min of operator's exposure - sensor carried by operator
5	N	4	> 25	< 8 h	enhanced general ventilation, LEV	indoor, 130 °C	9 mg/m³	0.60	Mean of 2011,2012 Measures : mean value of 8h operator exposure - sensor carried by operator
5	N	2	1 - 5	< 8 h	enhanced general ventilation, LEV	indoor, 90 °C	1.22 mg/m³	0.081	2013 Measure : full shift (8h) - sensor carried by the operator

ES	Source of data	PROC	Concen-tration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	RCR	Remarks on measured data (as provided by data source)
5	N	4	< 1	< 8 h	enhanced general ventilation, LEV	indoor, 50 °C	7 mg/m³	0.467	2012 Measure : mean value for full shift (8h) exposure - sensor carried by the operator
5	N	3	> 25	< 15 min	basic general ventilation, LEV	indoor, 70 °C	27 mg/m³	0.90	2013 Measure : mean value of 15 min of operator's exposure - sensor carried by operator
5	N	4	5 - 25	< 15 min	enhanced general ventilation, LEV	indoor, ambient temperature	10.5 mg/m³	0.35	Mean of 2012 Measure : mean value of 15 min of operator's exposure - sensor carried by operator
5	N	2	5 - 25	< 8 h	enhanced general ventilation, LEV	indoor, 90 °C	7.5 mg/m³	0.50	Mean of 2012 Measure : mean value for full shift (8h) exposure - sensor carried by the operator
5	N	4	1 - 5	< 1 h	LEV	indoor, ambient temperature	27 mg/m³	0.90	2012 Measure : mean value of 1 hour of operator's exposure - sensor carried by operator
5	O	4	5 - 25	< 8 h	basic general ventilation, LEV	indoor, ambient temperature	< 0.01 mg/m³	<0.01	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
5	O	5	> 25	< 1 h	basic general ventilation, LEV	indoor, ambient temperature	≤ 7.1 ppm [21.3 mg/m³]	0.71	maximum concentration
5	P	2	> 25	continuous	basic general ventilation, LEV	indoor, ambient temperature	0 - 2 ppm [0 – 6 mg/m³]	0.40	Concentration continuously monitored by fixed PID monitors. DMF detector tube readings are taken every shift.
6	L	8b	100	< 1 h	basic general ventilation, LEV	indoor, ambient temperature	0.8 mg/m³	0.053	DE concentration

ES	Source of data	PROC	Concen-tration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	RCR	Remarks on measured data (as provided by data source)
6	L	1	> 25	< 8 h	basic general ventilation, LEV	indoor, 100 °C	0.8 mg/m³	0.053	DE concentration
7	Q	1	> 25	< 15 min	basic general ventilation	indoor, 45 °C	< 0.3 mg/m³	0.02	The air concentration is reported as below the detection limit of the analytical method (< 0.3 mg/m³). The sampling was performed according to EN689 in active mode with a specific sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific absorbent for the sampling of the gaseous fraction. After the elution, the analysis was performed by GC-FID according to NF X 43-267 method. Number of measured data point: 3
7	Q	2	> 25	< 15 min	basic general ventilation	indoor, 45 °C	0.36 mg/m³	0.027	The air concentration is reported as below the detection limit of the analytical method (< 0.3 mg/m³). The sampling was performed according to EN689 in active mode with a specific sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific absorbent for the sampling of the gaseous fraction. After elution, the analysis was performed by GC-FID according to NF X 43-267 method. Number of measured data point: 3

ES	Source of data	PROC	Concen-tration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	RCR	Remarks on measured data (as provided by data source)
7	Q	3	> 25	< 15 min	basic general ventilation, LEV	indoor, 45 °C	< 0.3 mg/m³	0.02	The air concentration is reported as below the detection limit of the analytical method (< 0.3 mg/m³). The sampling was performed according to EN689 in active mode with a specific sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific absorbent for the sampling of the gaseous fraction. After elution, the analysis was performed by GC-FID according to NF X 43-267 method. Number of measured data point: 3
7	Q	7	> 25	< 4 h	basic general ventilation, LEV	indoor, 250 °C	< 0.3 mg/m³	0.02	The air concentration is reported as below the detection limit of the analytical method (< 0.3 mg/m³). The sampling was performed according to EN689 in active mode with a specific sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific absorbent for the sampling of the gaseous fraction. After elution, the analysis was performed by GC-FID according to NF X 43-267 method. Number of measured data point: 3
8	No measured data available								
9	No measured data available								

* basic general ventilation refers to 1 - 3 air changes per hour
good general ventilation refers to 3 - 5 air changes per hour
enhanced general ventilation refers to 5 - 10 air changes per hour
** Qualitative risk assessment was performed.

B.9.3 Article Assessment

Different types of articles used by industrial/professional workers and consumers are known to contain DMF residues. *In general, there is little information on concentration of DMF in articles and emissions from articles. However, due to widespread use of DMF in the plastic and related industry branches (e.g. artificial leather) outside EU, imported articles and consumer goods can contain relevant levels of DMF*. In the following, the different articles and their application are briefly described. Further information on the usage of these articles can be found in the relevant contributing scenarios.

Industrial / Professional Use

DMF residues in articles used by the industry sector were indicated for articles such as **gloves** and **acrylic fibres**. Zuther (2011) investigated DMF residues in PU-coated **gloves**. Concentrations between 2 mg/kg (0.0002 % w/w) and 3600 mg/kg (0.36 % w/w) were found in the different components (PU-coating; fabrics; etc.) of the investigated gloves. The highest concentrations were found in no-name Asian imports. High DMF concentrations in Asian products were also indicated by the SGS (2013a, 2013b) in two recent reports of analyses ordered by a British company on synthetic leather coming from Asia. DMF concentrations in PU cutting (PU/leather in black) were determined to be up to 16 212 mg/kg which corresponds to 1.6 % w/w. Other samples of leather and PU cuttings revealed DMF concentrations between 233 mg/kg (0.02 % w/w) and 6548 mg/kg (0.65 % w/w). Please refer to Annex B5 and Annex B6 for the full study reports. Specific information from the textile industry (company: Confidential information) further identified **acrylic fibres** to contain DMF residues in concentrations up to 1.5 % w/w.

Consumer Use

Some information referring to DMF residues in different articles have been made available recently in different publications. Greenpeace (2014) just published a study which deals with hazardous chemicals found in soccer World Cup merchandise. All twenty-one pairs of **football boots** were tested positive for DMF: Nineteen out of twenty-one football boots contained DMF at levels above 10 mg/kg (0.001 % w/w). Concentrations of DMF above 50 mg/kg (0.005 % w/w) were found in twelve football boots. However, specific concentration levels of the individual articles were not published by Greenpeace (2014).

Aside from DMF residues in football boots, DMF was also found in **slimy toys** by the Danish Ministry of the Environment (2005). In their survey of chemical substances in consumer products, 0.4 % m/m of DMF (percentage of totally collected VOC-content) have been found in one toy (hard plastic containers with green slime inside) of 14 toys tested.

B.9.3.1 Hazard assessment

In this subsection, the relevant DNELs are listed which have been used for calculation of the individual risk characterisation ratios. The exposure assessment concentrates on possible systemic effects after repeated exposure. Possible local effects are not expected due to the low concentration of DMF residues in articles. Further information on the hazard assessment can be found in section B.5 of the restriction dossier.

Worker DNELs

Scope and type of assessment

The scope of exposure assessment and type of risk characterisation required for workers are described in the following table based on the hazard conclusions presented in section B.5.11 of the restriction report.

Table B86. Type of risk characterisation required for workers.

Route	Type of effect	Type of risk characterisation	Hazard conclusion (see section 5.11)
Inhalation	Systemic, long-term	Quantitative	DNEL (Derived No Effect Level) = 15 mg/m³
Dermal	Systemic, long-term	Quantitative	DNEL (Derived No Effect Level) = 0.79 mg/kg bw/day

The industrial or professional worker comes into contact with DMF containing articles as a consequence of their professional life. In general the industrial/professional user is subject to national worker protection legislation (e.g. EU Chemical Agents Directive) and has residual risk controlled through control measures, which although a last line of defence, may include the use of Personal Protective Equipment (PPE).

Consumer DNELs

The scope of exposure assessment and type of risk characterisation required for consumers are described in the following table based on the hazard conclusions presented in section B.5.11 of the restriction report.

Table B87. Type of risk characterisation required for consumers.

Route	Type of effect	Type of risk characterisation	Hazard conclusion (see section 5.11)
Inhalation	Systemic, long-term	Quantitative	DNEL (Derived No Effect Level) = 15 mg/m³
Dermal	Systemic, long-term	Quantitative	DNEL (Derived No Effect Level) = 0.4 mg/kg bw/day
Oral	Systemic, long-term	Quantitative	DNEL (Derived No Effect Level) = 0.4 mg/kg bw/day

The consumer is unlikely to take informed measures to control exposure and to follow exactly the instructions for using articles. While using a specific product or article, consumers are mostly not aware of any existing risk. In addition, the non-professional pattern of use is expected to show a lower frequency and/or duration of use. Other default assumptions (i.e. decreased room volume) are more conservative compared to the risk assessment for workers. Another important aspect of consumer practice is the very limited use of PPE to control exposure. Consumers will not normally use PPE unless it is convincingly recommended by the manufacturer and provided with the product/article.

Referring to the risk characterisation, the calculated exposure levels are actually compared with the respective DNEL in order to estimate a potential risk. Since the DNELs are based on the Indicative Occupational Exposure Limit (OEL) Values, the risk characterisation for children needs to be slightly modified to account for this (more sensitive) population group. This was achieved by comparing the calculated exposure towards children with a 10 fold decreased DNEL.

B.9.3.2 Specific exposure limit values by existing legal requirements

EU legislation on the protection of health and safety of workers and consumers is spread over several pieces of legislation. In the following, the relevant existing legal requirements under EU legislation and other (national) regulations are listed and briefly described.

Regulation (EC) No 1907/2006 and **Regulation (EC) No 1272/2008**

Entry 30 of Annex XVII of the REACH Regulation for reprotoxic substances prohibits the placing on the market of the substance on its own or in preparations for sale to the general public in concentration equal to or greater than the relevant concentrations specified in Annex I to Directive 67/548/EEC or Directive 1999/45/EC. Given that, for DMF, there is no specific concentration limit in Part 3 of Annex VI of CLP Regulation, the relevant concentration which applies for this restriction is the cut-off value for reprotoxic substances of Directive 1999/45/EC, i.e. 0.5 % in weight. Thus, DMF should not be placed on the market or used for supply to the general public when the individual concentration is equal or above 0.5 % (weight/weight), as substance, as constituent of other substance or in a mixture (0.3 % after June 2015 according to section 3.7.3 of CLP Regulation (EC) No. 1272/2008).

Directive 2009/161/EC

An Indicative Occupational Exposure Limit Value (IOELV) for DMF has been established by Commission Directive 2009/161/EC of 17th December 2009 which describes the 3rd list of IOELVs in implementation of Council Directive 98/24/EC and amending Commission Directive 2000/39/EC. According to this Commission Directive, DMF air concentrations are limited to 15 mg/m³ (8h-TWA) and 30 mg/m³ (15 min-STEL). These limit values represent threshold levels of exposure below which, in general, no detrimental effects are expected after short-term or daily exposure over a working life time

Directive 2009/48/EC

The composition of toys is regulated by Directive 2009/48/EC. In Annex II (Part III – Chemical properties) it is clearly stated that substances that are classified as carcinogenic, mutagenic or toxic for reproduction (CMR) of category 1A, 1B or 2 under CLP Regulation (EC) No 1272/2008 shall not be used in toys, components of toys or in micro-structurally distinct parts of toys. However, by way of derogation substances or mixtures classified as CMR may be used in toys, in components of toys or micro-structurally distinct parts of toys if these substances and mixtures are contained in individual concentrations equal to or smaller than the relevant concentrations established in the CLP Regulation (EC) No 1272/2008 for the classification of mixtures containing these substances. According to the generic concentration limits of ingredients of a mixture classified as reproduction toxicants or for effects on or via lactation that trigger classification of the mixture in the CLP Regulation, a limit value of 0.5 % by mass (w/w) (0.3 % after June 2015 according to section 3.7.3 of CLP Regulation (EC) No. 1272/2008) is established which is also applied for the toys directive.

Directive 2001/95/EC

The General Product Safety Directive (GPSD) is intended to ensure a high level of product safety throughout the EU for consumer products that are not covered by specific sector legislation (e.g. toys, chemicals, cosmetics, machinery). The Directive also complements the provisions of sector legislation which do not cover certain matters, for instance in relation to producers' obligations and the authorities' powers and tasks. In addition to the basic requirement to place only safe products on the market, producers must inform consumers of the risks associated with the products they supply. They must take appropriate measures to prevent such risks and be able to trace dangerous products. The Member States are obliged to enforce the requirements on producers and distributors. They must appoint the authorities in charge of market surveillance and enforcement. In addition to the power to impose penalties, the Directive gives the surveillance authorities a wide range of monitoring and intervention powers. Under certain conditions, the Commission may adopt a formal Decision requiring the Member States to ban the marketing of a product posing a serious risk, to recall it from consumers or to withdraw it from the market. A Decision of this kind is only valid for a maximum of one year. To date, four Decisions of this kind have been taken at Community level. A decision referring to the dimethylformamide (CAS 68-72-2) content in products does not exist.
How Member States implemented this Directive into national legislation was not further investigated.

Pharma-Regulation

In 1990, limits for residual solvents were proposed in Pharmeuropa and, more recently, in the current guideline on residual solvents by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). In December 1997 the ICH published its Guidance for Industry Q3C which became effective in March 1998. ICH guideline compromised regulatory authorities from Europe, Japan and the United States, as well as representatives of the research based pharmaceutical industry. According to the latest ICH guideline Q3C (R5) on impurities (Guideline for residual solvents, August 2011), the substance dimethylformamide (CAS 68-72-2) is a class II solvent und and its content in pharmaceutical products is, thus, regulated. The permitted daily exposure (PDE) for DMF amounts to 8.8 mg/day which corresponds to a concentration limit of 880 ppm.

National limit values

Referring to DMF residues in articles, specific limit values have already been defined by different (national) authorities. The German Committee on Hazardous Substances set a maximum DMF limit value of 10 mg/kg (0.001 % w/w) for PU-coated gloves. This concentration limit is contained in the Technical Guideline for the handling of Hazardous Materials (TRGS 401, June 2008). The same limit was also set by the German Blue Angel eco-label for the use of DMF in shoes and protective gloves.

B.9.3.3 Exposure assessment and risk characterisation

By taking all this information into account, a risk assessment for the relevant articles is performed. The aim is to identify specific concentration levels in articles, which can be considered to be of acceptable risk for industrial/professional use and/or consumer applications.
For this purpose, different DMF concentrations (0.1, 0.3, 0.5 and 1.5 % w/w) were used as input parameter for the modelling approach in order to define cut-off values under which an unexpected risk for the relevant population (worker/general public) is expected.

Different modelling approaches have been used to estimate exposure of workers and consumers due to the usage of articles containing DMF residues. The approaches are described in detail as follows.

In order to guarantee an acceptable risk for workers and/or consumer, risk characterisation ratios for all exposure routes (incl. combined routes) need to be below the trigger value of 1. According to this approach, RCRs above this trigger value bear a potential and unacceptable risk. This was illustrated by the following color codes.

- Red: RCR ≥ 1 (unacceptable risk)
- Orange: RCR > 0.5 and < 1 (acceptable risk, seek reduction)
- Yellow: RCR > 0.1 and < 0.5 (acceptable risk)
- Green: RCR < 0.1 (acceptable risk)

B.9.3.3.1 Exposure modelling for industrial/professional use of articles

Referring to the information provided in ECHA REACH Guidance R.12 (March 2010) and the recently published CHESAR manual (ECHA, 2014), applications associated with the service-life of articles at industrial sites are characterised by PROC 21, PROC 22, PROC 23, PROC 24 and PROC 25. These processes mainly describe the handling of metals. Hence, the usage of DMF containing articles by the industry sector cannot be defined by these process categories. Consecutively, modelling tools such as ECETOC TRA which estimate worker exposure based on the relevant process categories cannot be applied.

Usage of gloves containing DMF

In order to perform an adequate risk assessment, equations with simple algorithms are applied which are mainly used for estimating consumer exposure. Nevertheless, sufficient and reliable exposure calculations can be performed by modifying the default equations in accordance with the relevant contributing scenario and its conditions of use. Exposure calculations for workers handling articles with DMF content of 0.1 % w/w and 0.3 % w/w are exemplary performed. Calculations for articles containing DMF residues in higher amounts can be undertaken analogously.

Handling of acrylic fibres (post-processing)

In order to perform an adequate risk assessment, equations with appropriate algorithms are applied which are in compliance with ECETOC TRA. Nevertheless, sufficient and reliable exposure calculations can only be performed by modifying the default equations in accordance with the relevant contributing scenario and its conditions of use. Exposure calculations for workers handling acrylic fibres with a DMF content of 1.5 % w/w were performed as described in B.9.3.3.1.2.

B.9.3.3.1.1 Worker contributing scenario 1: Use of gloves

This contributing scenario describes the usage of gloves (i.e. PU coated gloves), containing DMF residues, by industrial and/or professional worker. It is assumed that the gloves have a total weight of 50 g. During one working day (8 hour), usage of three different pairs of gloves is taken into consideration. The worker has a total weight of 70 kg (default value for workers).

Conditions of use (industrial gloves)

Conditions for dermal route of exposure (industrial gloves)

A dermal transfer factor of 1 is additionally taken into account. Conclusions drawn for the toxicokinetic behaviour of the substance show that the substance is readily absorbed via all exposure routes in humans.

Migration studies on the release of DMF from gloves have been conducted by Zuther (2011). For this purpose, gloves have been kept in a solution of synthetic perspiration at 37 °C for 8 hours. As final result, 70 to 100 % of DMF migrated into the perspiration solution depending on the DMF concentration in the article. By taking the assumed conditions of use (i.e. two pairs of gloves used per day) and migration rate dependencies (i.e. concentration of DMF in the article, amount and distribution of perspiration) into account, a migration rate of 70 % is sufficiently justified for a reasonable worst-case assumption. This results in an exposure reduction factor of 0.7 for dermal exposure.

According to ECHA REACH Guidance R.15 (Equation R.15-4, October 2012), the dermal dose can be calculated by the following equation (assumption: DMF residues of 0.1 % w/w).

Equation R.15-4: $D_{der} = \frac{Q_{prod} \cdot FC_{prod} \cdot n}{BW} \cdot 1000$	
D_{der}	Amount of substance (external dose) that can potentially be taken up (account later for actual dermal absorption) per body weight [mg /kg bw/day]
Q_{prod}	Amount of undiluted product used [g]
Fc_{prod}	Weight fraction of substance in the product [-]
n	Number of applications [-]
BW	Body weight [kg]

This equation leads to the following exposure estimation for dermal route of exposure:

D_{der} = ((30g x 0.001 x 2) / 70 kg) x 1000 = 0.857 mg/kg bw/day.

By taking the migration rate for DMF into account (see section above), the equation is slightly modified as follows:

D_{der} = ((30g x 0.001 x 2 x **0.7**) / 70 kg) x 1000 = **0.6 mg/kg bw/day.**

Conditions for inhalative route of exposure (industrial gloves)

For estimating inhalation exposure, it is assumed that 20 workers are situated in a production hall of 2000 m³ at the same time. As described for estimating dermal exposure, each worker is expected to use two pairs of gloves per work-shift. Additionally, 70 % of DMF contained in gloves does migrate into perspiration where it is taken up by the skin. Hence, only 30 % of the DMF residues can be released into the air of the working place (reduction factor: 0.3).

Since additional reduction factors are not included in the applied equation (see below), this had to be refined manually in order to account for industrial hygiene standards. As a consequence, a reduction factor of 0.1 (90 % effectiveness) for the Local Exhaust Ventilation (LEV) is additionally applied.

According to ECHA REACH Guidance R.15 (Equation R.15-1, October 2012), the air concentration can be calculated by the following equation (assumption: DMF residues of 0.1 % w/w).

Equation R.15-1:

$$C_{inh} = \frac{Q_{prod} \cdot Fc_{prod}}{V_{room}} \cdot 1000$$

C_{inh}	Concentration of substance in air of room [mg/m³]
Q_{prod}	Amount of undiluted product used [g]
Fc_{prod}	Weight fraction of substance in the product [-]
V_{room}	Room size [m³]

This equation leads to the following exposure estimation for inhalation route of exposure:

C_{inh} = ((1200g x 0.001) / 2000 m³) x 1000 = 0.6 mg/m³

By taking the migration rate and additional reduction factors for DMF into account (see section above), the equation is slightly modified as follows:

C_{inh} = ((1200g x 0.001 x **0.3**) / 2000 m³) x 1000 x **0.1** = **0.018 mg/m³**

Exposure and risks for workers (industrial gloves)

The exposure concentrations and risk characterisation ratios (RCRs) for the industrial use of articles containing DMF residues (industrial use of gloves) are reported in the following table. Maximum DMF concentrations in gloves were identified as 0.36 % (w/w). In PU cuttings, even concentrations up to 1.6 % (w/w) were reported (please refer to section B.9.3).

Table B88. Industrial gloves: Exposure concentrations and risks for workers (0.1 % w/w).

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.018 mg/m³** (Equation R.15-1)	RCR < 0.1
Dermal, systemic, long-term	**0.6 mg/kg bw/day** (Equation R.15-4)	RCR = 0.759
Oral, systemic, long-term	not relevant	not applicable
Combined routes, systemic, long-term		RCR = 0.761

Table B89. Industrial gloves: Exposure concentrations and risks for workers (0.3 % w/w)

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.054 mg/m³** (Equation R.15-1)	RCR < 0.1
Dermal, systemic, long-term	**1.8 mg/kg bw/day** (Equation R.15-4)	RCR = 2.278
Oral, systemic, long-term	not relevant	not applicable
Combined routes, systemic, long-term		RCR = 2.282

Conclusion on risk characterisation (industrial gloves)

The concentration of 0.1 % w/w of DMF is considered to be of acceptable risk for industrial workers. An increased DMF content (i.e. 0.3 % w/w) in the article leads to an increased exposure by factor 3 resulting in an unacceptable risk for workers. Conclusively, the DMF limit value of 10 mg/kg (0.001 % w/w) for protective gloves set by the German Committee on Hazardous Substances is considered to be sufficient to ensure an adequate control of risk. The results can also be assigned for professional workers. Although professionals may have less strict Risk Management Measures implemented (i.e. no application of LEV), the usage of DMF containing gloves (DMF concentration of 0.1 % w/w) is considered to be of acceptable risk. Referring to the conditions of use, professionals are not expected to use two pairs of gloves daily which are worn for a full and complete working-shift.

B.9.3.3.1.2 Worker contributing scenario 2: Use of acrylic fibres

This contributing scenario describes the usage (post-processing) of acrylic fibres containing DMF residues up to 1.5% by industrial workers. During one working day, workers are not longer exposed to the substance than 1 hour since most processes are performed automatically. Only manual transfer processes of acrylic fibres could result in a DMF exposure via dermal and/or inhalation route. Based on site specific information, not more than 20 events/day take place. For workers, a body weight of 70 kg (default value for workers) is taken into account.

Conditions of use (industrial fibres)

After finishing processes of the acrylic fibres, further processing (dyeing procedures) of these fibres takes place. In general, acrylic fibres can be obtained in different forms such as staple fibre, fully relaxed fibre and tow type. The dying process of these fibres (e.g. as yarn or knitted material) is performed in an aqueous solution by using cationic dyes. The ratio of fibre to water depends on the relevant dyeing procedure and might amount from 1:4 to 1:20. Process temperatures between 98 °C and 104 °C need to be achieved during these treatments in order to ensure the fixation of the dye. Those processes take place for 15 – 60 minutes depending on the required color depth. During the dyeing process, DMF contained in the acrylic fibres dissolves in the aqueous solution and is further diluted due to different rinsing processes. After the dyeing procedure, fibres contain DMF well below 0.1 % w/w.

In exceptional cases, the raw material (undyed acrylic fibres) might be used for post-processing purposes. For this reason, blind dyeing methods are applied. These processes have similar conditions as described above. Only the duration of this "dyeing process" as well as the process temperature is slightly modified (ca. 15 minutes at 98 °C). This procedure also leads to a DMF concentration in the final product well below 0.1 % w/w.

In general, the dyeing procedures are performed in an automated and closed process. Cleaning and maintenance activities are automated as well. Technical measures such as increased natural ventilation and Local Exhaust Ventilation are expected to be quite efficient for DMF exposure reduction. DMF exposure during post-processing of acrylic fibres is only expected to be relevant during transfer processes of the acrylic fibres.

Exposure and risks for workers (industrial fibres)

Inhalation exposure (industrial fibres)

For estimating inhalation exposure, it is assumed that 5 kg of acrylic fibres are transferred per event. This application takes place around 20 times and is only performed by one worker for not longer than 1 h/day in total. The industrial worker is situated in a production hall of 2000 m³. These assumptions are also based on site specific information. The fraction of DMF released to air is negligible due to the strong fixation of the substance into the fibre matrix (please refer to subsection below). As done for the dermal transfer factor, 0.1 % release to air is assumed which describes a worst-case approach. According to the DMF measurements of the textile industry, no significant amounts of DMF are released.

Since additional reduction factors are not included in the applied equation (see below), this had to be refined manually in order to account for industrial hygiene standards. As a consequence, a reduction factor of 0.1 (90 % effectiveness) for the Local Exhaust Ventilation (LEV) is additionally applied.

According to ECETOC Technical Report No. 107 (Section 3.1.2.2, 2009), the air concentration can be calculated by the following equation (assumption: DMF residues of 1.5 % w/w).

Equation for calculating inhalation exposure (ECETOC Technical Report No. 107, 2009):

Parameter:	Product Ingredient (g/g)	Amount product used per application (g/event)	FreQuency of use (events/day)	Fraction released to air[1] g/g)	Exposure Time (h)	Inhalation Rate (m³/h)	Conversion Factor	Room Volume (m³)	Body Weight (kg)	Expo-sure (mg/kg/d)	Expo-sure (mg/m³)
Algorithm:	(PI x	A x	FQ x	F x	ET x	IR x	1000)	V x	BW		

This equation leads to the following exposure estimation for dermal route of exposure:

D_{inh} = (0.015 g/g x 5000 g x 20 events/day x 0.001 g/g x 1 h x 1.25 m³/h x 1000) / (2000 m³ x 70 kg) = 0.013 mg/kg bw/day.

which corresponds to

0.013 mg/kg bw/day x 70 kg / 10 m³/day = 0.094 mg/m³

By taking additional reduction factors for DMF into account (LEV, see section above), the equation is

slightly modified as follows:

D_{inh} = (0.015 g/g x 5000 g x 20 events/day x 0.001 g/g x 1 h x 1.25 m³/h x 1000 x **0.1**) / (2000 m³ x 70 kg) = 0.001 mg/kg bw/day.

which corresponds to

0.001 mg/kg bw/day x 70 kg / 10 m³/day = **0.009 mg/m³**

Remark: For the described contributing scenario, DMF concentrations in air have already been monitored. However, these measured data are not yet available. Consecutively, exposure values have been calculated instead.

Dermal exposure (industrial fibres)

Since the substance is fixed in the acrylic fibre matrix, a reliable transfer factor needs to be taken into account as well. It is estimated that the dermal transfer factor from the article to the skin is equal or less than 0.001 which corresponds to 0.1 %. This assumption is based on DMF measurements in acrylic fibres after several washing procedures (up to 60 °C) according to DIN EN ISO 6330 (please refer to Annex B7). It was clearly shown that no significant amounts of DMF have been released into the washing solution during the handling and treatment. Thus, strong fixation of DMF to the fibre matrix was confirmed. In order to account for measuring uncertainties, a release factor of 0.1 % was assumed which definitely represents a worst-case approach here since no release at all has been determined.

According to ECETOC Technical Report No. 107 (Section 3.1.2.1, 2009), the dermal dose can be calculated by the following equation (assumption: DMF residues of 1.5 % w/w).

Equation for calculating dermal exposure (ECETOC Technical Report No. 107, 2009):

Parameter:	Product Ingredient (g/g)	Contact Area (cm²)	FreQuency of use (events/day)	Thickness of Layer (cm)	Density (g/cm³)	Conversion Factor (mg/g)	Body Weight (kg)	Exposure (mg/kg/d)
Algorithm:	(PI x	CA x	FQ x	TL x	D x	1000)	/ BW	

This equation leads to the following exposure estimation for dermal route of exposure:

D_{der} = (0.015g/g x 430 cm² x 20 events/day x 0.01 cm x 0.94 g/cm³ x 1000) / 70 kg = 17.32 mg/kg bw/day.

Since this equation assumes 100% transfer of substance from the product or article to the skin without applying any transfer factor, further refinements are necessary to adequately estimate exposure.

By taking a transfer factor of 0.001 (0.1%) for DMF into account (see section above), the equation is slightly modified as follows:

D_{der} = (0.015g/g x **0.001** x 430 cm² x 20 events/day x 0.01 cm x 0.94 g/cm³ x 1000) / 70 kg = **0.017 mg/kg bw/day.**

Remark: In the described contributing scenario, no gloves have been used for dermal exposure reduction.

Exposure and risks for workers (industrial acrylic fibres)

The exposure concentrations and risk characterisation ratios (RCRs) for the industrial use of articles containing DMF residues (industrial use of acrylic fibres) are reported in the following table. DMF concentrations up to 1.5 % (fixed in matrix) have been assessed to bear an acceptable risk towards human health.

Table B90. Industrial acrylic fibres: Exposure concentrations and risks for workers (1.5 % w/w).

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.009 mg/m³** (ECETOC approach)	RCR < 0.1
Dermal, systemic, long-term	**0.017 mg/kg bw/day** (ECETOC approach)	RCR < 0.1
Oral, systemic, long-term	not relevant	not applicable
Combined routes, systemic, long-term		RCR < 0.1

B.9.3.3.2 Exposure modelling for consumer use of articles

According to ECHA REACH Guidance R.15 (Consumer Exposure Estimation, October 2012), **ECETOC TRA v3** for consumers combines the conservatism of a first Tier assessment tool with the expert knowledge documented in the ConsExpo fact sheets. The tool aims to balance the Tier 1 assumptions and the generic applicability to a wide range of product categories in order to deliver reasonably plausible outcomes.

With regard to **football boots,** a suitable subcategory as predefined within ECETOC TRA v3 could be identified as follows:

- Football shoes: AC 10 (Rubber products) with subcategory “Footwear (shoes, boots)” and/or AC 6 (Leather articles) with subcategory “Footwear (shoes, boots)”

In order to account also for the usage of football boots by children, a second subcategory was defined manually within the model. This subcategory takes relevant parameters into account which need to be applied for assessing exposure of children (specific skin contact area and reduced body weight). All relevant input parameter are described in the relevant contributing scenarios.

A specific and predefined subcategory for **gloves** could not be identified in the modelling tool. Consecutively, a subcategory was manually defined for AC 10 (rubber products). As mentioned above, all relevant modelling parameters are listed and explained in the corresponding contributing scenario.

For modelling exposure due to the usage of **slimy toys**, neither a specific article category nor a relevant subcategory could be identified, which hindered an adequate and reliable exposure modelling for this article using ECETOC TRA v3. Although the assessment of toys can be applied in the modelling software, only rubber toys, plastic toys, wooden toys and cuddly toys can be assessed. Due to the specific consistency of slimy toys, another exposure modelling tool had to be used.

Thus, a different TRA using **ConsExpo v5.0** was performed. This software tool is also recommended in ECHA REACH Guidance R.15 (October 2012) for consumer exposure modelling. Due to the fact that

specific default scenarios for children's toys are predefined within the relevant ConsExpo factsheet, this approach is considered as most suitable to perform the relevant exposure estimations. In order to estimate exposure from the usage of slimy toys, two predefined scenarios (usage of modelling clay; application of finger paint) were considered in detail in order to identify the best suitable input parameters to accurately estimate exposure. As mentioned above, all relevant modelling parameters are listed and explained in the corresponding contributing scenario. In general, the calculated values for exposure and uptake will result in a 99th percentile (reasonable worst-case estimation).

B.9.3.3.2.1 Consumer contributing scenario 1: Use of sports shoes (AC 10-3) - Adults

This contributing scenario describes the usage of sports shoes containing DMF residues by adults. It is assumed that the shoes have a total weight of 800 g and are daily used for 8 hours. The consumer has a total weight of 60 kg (default value for females) and is potentially exposed to the article with a specific skin surface area of around 2000 cm² (hands and feet). These conditions are predefined in ECETOC TRA v3 within the article subcategory. These parameters clearly represent a conservative approach (i.e. worst-case).

Further conditions for dermal route of exposure (sports shoes – adult)

The dermal transfer factor was set to 1 (worst-case). For exposure from articles via the dermal route, the assumed thickness of layer in contact with skin is reduced from 0.01 cm (widely accepted default for mixtures and used already in EU existing chemicals risk assessment procedures) to 0.001 cm in order to take account of the reduced mobility of substances in an article matrix.

Conditions for inhalation exposure (sports shoes – adult)

In order to estimate inhalation exposure, indoor application is assumed. Therefore, a room volume of 20 m³ and an air dilution factor of 0.172 (ECETOC TRA default values) were taken into consideration.

Conditions for oral route of exposure (sports shoes – adult)

Oral contact is not foreseen for this contributing scenario. Even oral exposure via hand-mouth contact is considered as negligible because the substance is fixed in a matrix. However, intensive hand-mouth contact will be assessed in the consumer contributing scenario 2 dealing with the usage of sports shoes by toddlers.

Conditions of use (sports shoes – adult)

	Method
Product (article) characteristics	
• Article category: AC 10 (Rubber products)	ECETOC TRA v3
• Article subcategory: Footwear (shoes, boots)	ECETOC TRA v3
• Concentration of substance in mixture: - 0.001 g/g - 0.003 g/g **Remark**: The article subcategory was assessed twice by assuming different concentrations of DMF residues (0.1 %, 0.3 % w/w), respectively.	ECETOC TRA v3
• Oral contact foreseen: No	ECETOC TRA v3
Amount used, frequency and duration of use/exposure	
• Amount of product used per application: = 800 g/event	ECETOC TRA v3
• Exposure time: = 8 hr	ECETOC TRA v3

	Method
• Frequency of use: = 1 events/day	ECETOC TRA v3
Other conditions affecting consumers exposure	
• Body parts potentially exposed: Hands and forearms (2082.5 cm²) **Remark**: Specific skin surface areas are defined within ECETOC TRA v3 and cannot be modified. With regard to the usage of sports shoes, exposure to hands (fronts; backs) and feet is considered as relevant. According to US EPA (1997, cited in ECHA REACH Guidance R.15), the mean surface area (men) for hands and feet amounts to 1960 cm². This value is comparable to the above mentioned value used for the exposure assessment.	ECETOC TRA v3
• Dermal transfer factor: = 1	ECETOC TRA v3
• Thickness of layer: = 0.001 cm	ECETOC TRA v3
• Room volume: = 20 m³	ECETOC TRA v3
• Body weight: = 60 kg	ECETOC TRA v3
• Dilution factor (air): = 0.172	ECETOC TRA v3

Exposure and risks for consumers (sports shoes – adult)

The exposure concentrations and risk characterisation ratios (RCR) for sport shoes containing different concentrations of DMF residues are reported in the following tables. According to ECHA REACH Guidance R.15, the algorithm for the calculation of the dermal dose does not take into account any duration factor and assumes 100 % transfer of substance from the product or article contact layer to the skin instantaneously.

Table B91. Sports shoes – aduld: Exposure concentrations and risks for consumers (0.1 % w/w).

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**6.897 mg/m³** (ECETOC TRA v3)	RCR = 0.460
Dermal, systemic, long-term	**0.035 mg/kg bw/day** (ECETOC TRA v3)	RCR = 0.088
Oral, systemic, long-term	not relevant	not applicable
Combined routes, systemic, long-term		RCR = 0.548

Table B92. Sports shoes – aduld: Exposure concentrations and risks for consumers (0.3 % w/w).

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**20.690 mg/m³** (ECETOC TRA v3)	RCR = 1.379
Dermal, systemic, long-term	**0.104 mg/kg bw/day** (ECETOC TRA v3)	RCR = 0.260
Oral, systemic, long-term	not relevant	not applicable
Combined routes, systemic, long-term		RCR = 1.639

Conclusion on risk characterisation (sports shoes – adult)

The concentration of 0.1 % w/w of DMF is considered as safe for football boots. An increased DMF content (i.e. 0.3 % w/w) in the article would lead to an increased exposure resulting in an unacceptable risk for workers with RCRs > 1.

B.9.3.3.2.2 Consumer contributing scenario 2: Use of sports shoes (AC 10-3) - Toddlers

This contributing scenario describes the usage of sports shoes containing DMF residues by toddlers. It is assumed that the shoes have a total weight of 200 g and are daily used for 8 hours. The child has a total weight of 10 kg (default value for children) and is potentially exposed to the article with a specific skin surface area of around 560 cm² (hands and feet). These conditions are based on the predefined conditions associated with the article subcategory within ECETOC TRA v3. For this purpose, the predefined conditions (total amount of article, weight of consumer, skin surface area) were slightly modified to account for toddlers. This exposure modelling approach is also quite conservative assuming that a child is wearing the same sports boots every day for 8 hours.

Further conditions for dermal and inhalation route of exposure (sports shoes – toddler)

The basic set of default parameters for dermal exposure (i.e. dermal transfer factor, thickness of layer) and inhalation exposure (i.e. room volume, dilution factor) are identical to the ones described in the previous consumer contributing scenario. Specific parameters referring to the exposure assessment of toddlers are mentioned in the section above.

Conditions for oral route of exposure (sports shoes – toddler)

Oral contact is foreseen for this contributing scenario. Intensive hand-mouth contact is assessed by assuming a skin surface area of around 172 cm² which is mouthed. This represents the highest skin contact area which can be assumed for oral exposure using ECETOC TRA v3.

Conditions of use (sports shoes – toddler)

	Method
Product (article) characteristics	
• Article category: AC 10 (Rubber products)	ECETOC TRA v3
• Article subcategory: Footwear (shoes, boots)	ECETOC TRA v3
• Concentration of substance in mixture: 0.001 g/g	ECETOC TRA v3
• Oral contact foreseen: Yes	ECETOC TRA v3
Amount used, frequency and duration of use/exposure	
• Amount of product used per application: = 200 g/event	ECETOC TRA v3
• Exposure time: = 8 hr	ECETOC TRA v3
• Frequency of use: = 1 events/day	ECETOC TRA v3
Other conditions affecting consumers exposure	
• Body parts potentially exposed: Hands and forearms (556.8 cm²) **Remark**: Specific skin surface areas are defined within ECETOC TRA v3 and cannot be modified. With regard to the usage of sports shoes, exposure to hands (fronts; backs) and feet is considered as relevant. According to RIVM (2006, cited in Nordic Exposure Group, 2011), the mean surface area (children aged 1.5 years) for hands and feet amounts to 564 cm². This value is comparable to the above mentioned value used for the exposure assessment.	ECETOC TRA v3

	Method
• Dermal transfer factor: = 1	ECETOC TRA v3
• Thickness of layer: = 0.001 cm	ECETOC TRA v3
• Room volume: = 20 m³	ECETOC TRA v3
• Body weight: = 10 kg	ECETOC TRA v3
• Dilution factor (air): = 0.172	ECETOC TRA v3
• Selected surface area mouthed: inside one hand, all fingers (127.2 cm²)	ECETOC TRA v3

Exposure and risks for consumers (sports shoes – toddler)

The exposure concentrations and risk characterisation ratios (RCR) for sport shoes containing different concentrations of DMF residues are reported in the following tables. As previously mentioned, the estimated exposure values are compared with modified DNELs (decreased by a factor of 10) to account for this (more sensitive) subpopulation. Consecutively, exposure values are compared with a $DNEL_{inh}$ of 1.5 mg/m³, a $DNEL_{der}$ of 0.04 mg/kg bw/day and a $DNEL_{oral}$ of 0.04 mg/kg bw/day.

Table B93. Sport shoes – toddler: Exposure concentrations and risks for consumers (0.1 % w/w).

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.724 mg/m³** (ECETOC TRA v3)	RCR = 1.15
Dermal, systemic, long-term	**0.056 mg/kg bw/day** (ECETOC TRA v3)	RCR = 1.40
Oral, systemic, long-term	**0.013 mg/kg bw/day** (ECETOC TRA v3)	RCR = 0.325
Combined routes, systemic, long-term		RCR = 2.875

Conclusion on risk characterisation (sports shoes – toddler)

The concentration of 0.1 % w/w of DMF in sport boots used by toddlers is considered to bear a potential risk towards human health. This also applies for DMF concentrations of > 0.1 % w/w.

B.9.3.3.2.3. Consumer contributing scenario 3: Use of gloves (AC 10) - Adults

This contributing scenario describes the usage of gloves containing DMF residues by adults. It is assumed that the gloves have a total weight of 50 g (one pair). Two pairs of gloves are used daily for 2 hours, respectively. The consumer has a total weight of 60 kg (default value for females) and is potentially exposed to the article with a specific skin surface area of around 858 cm² (hands, fronts and backs).

Further conditions for dermal route of exposure (gloves – adult)

The dermal transfer factor was set to 1 (worst-case). For exposure from articles via the dermal route, the assumed thickness of layer in contact with skin is reduced from 0.01 cm (widely accepted default for mixtures and used already in EU existing chemicals risk assessment procedures) to 0.001 cm in order to take account of the reduced mobility of substances in an article matrix.

Conditions for inhalation exposure (gloves – adult)

In order to estimate inhalation exposure, indoor application is assumed. Therefore, a room volume of 20 m^3 and an air dilution factor of 0.172 (ECETOC TRA default values) were taken into consideration.

Conditions for oral route of exposure (gloves – adult)

Oral contact is foreseen for this contributing scenario. Hand-mouth contact is assessed by assuming a skin surface area of around 36 cm^2 which is mouthed (some fingertips).

Conditions of use (gloves – adult)

	Method
Product (article) characteristics	
• Article category: AC 10 (Rubber products)	ECETOC TRA v3
• Article subcategory: not assigned	ECETOC TRA v3
• Concentration of substance in mixture: - 0.001 g/g - 0.003 g/g - 0.005 g/g **Remark**: The article subcategory was assessed thrice by assuming different concentrations of DMF residues (0.1 %, 0.3 % and 0.5 % w/w), respectively.	ECETOC TRA v3
• Oral contact foreseen: Yes	ECETOC TRA v3
Amount used, frequency and duration of use/exposure	
• Amount of product used per application: = 50 g/event	ECETOC TRA v3
• Exposure time: = 4 hr (2 x 2 hr)	ECETOC TRA v3
• Frequency of use: = 2 events/day	ECETOC TRA v3
Other conditions affecting consumers exposure	
• Body parts potentially exposed: Hands (857.5 cm^2)	ECETOC TRA v3
• Dermal transfer factor: = 1	ECETOC TRA v3
• Thickness of layer: = 0.001 cm	ECETOC TRA v3
• Room volume: = 20 m^3	ECETOC TRA v3
• Body weight: = 60 kg	ECETOC TRA v3
• Dilution factor (air): = 0.172	ECETOC TRA v3
• Selected surface area mouthed: some fingertips (35.7 cm^2)	ECETOC TRA v3

Exposure and risks for consumers (gloves – adult)

The exposure concentrations and risk characterisation ratios (RCR) for gloves containing different concentrations of DMF residues are reported in the following tables.

Table B94. Gloves – adult: Exposure concentrations and risks for consumers (0.1 % w/w).

Route of exposure and type of effects	**Exposure concentration**	**Risk characterisation**
Inhalation, systemic, long-term	**2.273 mg/m³** (ECETOC TRA v3)	RCR = 0.152

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Dermal, systemic, long-term	**0.172 mg/kg bw/day** (ECETOC TRA v3)	RCR = 0.430
Oral, systemic, long-term	**0.007 mg/kg bw/day** (ECETOC TRA v3)	RCR = 0.018
Combined routes, systemic, long-term		RCR = 0.600

Table B95. Gloves – adult: Exposure concentrations and risks for consumers (0.3 % w/w)

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**6.818 mg/m³** (ECETOC TRA v3)	RCR = 0.455
Dermal, systemic, long-term	**0.515 mg/kg bw/day** (ECETOC TRA v3)	RCR = 1.288
Oral, systemic, long-term	**0.021 mg/kg bw/day** (ECETOC TRA v3)	RCR = 0.053
Combined routes, systemic, long-term		RCR = 1.796

Table B96. Gloves – adult: Exposure concentrations and risks for consumers (0.5 % w/w)

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**11.364 mg/m³** (ECETOC TRA v3)	RCR = 0.758
Dermal, systemic, long-term	**0.858 mg/kg bw/day** (ECETOC TRA v3)	RCR = 2.145
Oral, systemic, long-term	**0.036 mg/kg bw/day** (ECETOC TRA v3)	RCR = 0.090
Combined routes, systemic, long-term		RCR = 2.993

Conclusion on risk characterisation (gloves – adult)

DMF residues in a concentration of 0.1 % w/w in gloves are considered to be of acceptable risk for consumers. The combined RCR is below the trigger value of 1. A concentration of 0.3 % w/w leads to a potential risk for human health. This assumption is based on the combined RCR which amounts to 1.796.
The results for the consumer use of gloves are similar to the results for the industrial use of gloves. However, for industrial use of DMF containing gloves the dermal exposure route is more critical. This is mainly based on the amount of gloves used daily. Contrary, for consumer use of gloves the inhalation exposure is more critical. Referring to exposure calculations for consumers, a relatively small room volume (20 m³) is assumed for the modelling which explains this critical exposure route.

B.9.3.3.2.4 Consumer contributing scenario 4: Use of slimy toys – Toddlers

This contributing scenario describes the usage of slimy toys containing DMF residues by toddlers. It is assumed that the slimy toy has a total weight of 200 g (estimated). Furthermore, it is expected that a

slimy toy is used 100 times per year for a duration of 60 minutes (default values for modelling clay and finger paint; Bremmer and van Veen, 2002). The child has a total weight of 12.5 kg (ConsExpo default value for a 3 year old child; Bremmer et al., 2006) and is potentially exposed to the article with a specific skin surface area of around 318 cm² (estimated for 3 year old child, fronts and backs). Due to the fact that toys such as slimy toys are age-restricted, default values for a 3 year old child were considered for the risk assessment.

Further conditions for dermal route of exposure (slimy toys – toddler)

The dermal transfer factor was set to 1 (worst-case). As dermal subscenario, instant application was used. This subscenario is defined within the ConsExpo tool assuming that the product is applied at once to the skin.

Conditions for inhalation exposure (slimy toys – toddler)

In order to estimate inhalation exposure, indoor application is assumed. Therefore, a room volume of 20 m³ and an air change per hour of 0.6 (ConsExpo default values; Bremmer and van Veen, 2002) were taken into consideration. As inhalation subscenario, exposure to vapour during instantaneous release was assessed. This scenario is also defined within the modelling tool and assumes that the substance is completely released from the product at once in a room.

Conditions for oral route of exposure (slimy toys – toddler)

Oral contact is foreseen for this contributing scenario. Due to intensive hand-mouth contact as expected for children and the special consistency of the product (viscous), it was assumed that oral exposure to the product occurs at a constant rate of 30 mg/min (default value for finger paints; Bremmer and van Veen, 2002) for a duration of 60 minutes.

Conditions of use (slimy toys – toddler)

	Method
Product (article) characteristics	
• Article category: not applicable	Cons Expo v5
• Article subcategory: not applicable	Cons Expo v5
• Concentration of substance in mixture: - 0.001 g/g	Cons Expo v5
• Oral contact foreseen: Yes (intensive hand-mouth contact)	Cons Expo v5
Amount used, frequency and duration of use/exposure	
• Amount of product used per application: = 200 g/event	Cons Expo v5
• Exposure time: = 60 min	Cons Expo v5
• Frequency of use: = 100 times/year	Cons Expo v5
Other conditions affecting consumers exposure	
• Body parts potentially exposed: Hands (318 cm²)	Cons Expo v5
• Dermal transfer factor: = 1	Cons Expo v5
• Room volume: = 20 m³	Cons Expo v5
• Body weight: = 12.5 kg	Cons Expo v5
• Air changes per hour: = 0.6	Cons Expo v5
• Mode of release (inhalation): Instantaneous release (All the chemical is released at once in the room.)	Cons Expo v5

	Method
Inhalation uptake fraction: 1	
• Dermal loading: Intensive hand-mouth contact (ingestion by constant rate of 30 mg/min for 60 min)	Cons Expo v5
• Oral ingestion model: ingestion at a constant rate (30 mg/min) Oral uptake fraction: 1	Cons Expo v5

Exposure and risks for consumers (slimy toys – toddler)

The exposure concentrations and risk characterisation ratios (RCR) for slimy toys are reported in the following tables. As previously mentioned, the estimated exposure values are compared with modified DNELs (decreased by a factor of 10) to account for this (more sensitive) subpopulation. Consecutively, exposure values are compared with a $DNEL_{inh}$ of 1.5 mg/m³, a $DNEL_{der}$ of 0.04 mg/kg bw/day and a $DNEL_{oral}$ of 0.04 mg/kg bw/day.

Table B97. Slimy toys – toddler: Exposure concentrations and risks for consumers (0.1 % w/w).

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.082 mg/m³** (Cons Expo v5)	RCR < 0.1
Dermal, systemic, long-term	**4.2 mg/kg bw/day** (Cons Expo v5)	RCR = 105
Oral, systemic, long-term	**0.038 mg/kg bw/day** (Cons Expo v5)	RCR = 0.95
Combined routes, systemic, long-term		RCR = 106

Conclusion on risk characterisation (slimy toys – toddler)

This modelling approach definitely shows that DMF residues of 0.1 % w/w are not of acceptable risk for consumers (subpopulation: toddlers).

B.9.3.4 Overall conclusions

Exposure modelling was performed for some user groups (industrial/professional worker, consumer) handling articles which are known to contain DMF residues. Different DMF concentrations (0.1, 0.3, 0.5 and 1.5 % w/w) were considered in detail in order to define specific cut-off values. If these trigger values are not exceeded, an acceptable risk for the relevant user group is expected (RCR < 1). The final results for articles used by the industry and consumers will be briefly summarized in the following subsections. Furthermore, the reliability of the applied software tools and the validity of the estimated exposure values will be discussed.

An overview table with all related RCR values associated with industrial/professional and consumer use of DMF containing articles is provided in Section F.1.3 (Table F9).

Articles which are used by industrial worker

It was shown in the relevant contributing scenario that PU coated **gloves** containing 0.1 % DMF are of acceptable risk for industrial workers. These results were also assigned for professionals. Concentrations above this trigger value (i.e. 0.3 % w/w) bear a potential (unacceptable) risk for human health.

Reliability of the modelling and validity of estimated exposure values

Referring to the calculations for the industrial use of gloves containing DMF, equations using simple algorithms were applied. According to the ECETOC Technical Report No. 58 (ECETOC Targeted Risk Assessment, 1994), the use of default values in the absence of data may often lead to an overestimation of the exposure dose. A check for realism in the exposure assessment is therefore recommended to ensure that the final assessment is realistic and not overly conservative. In order to guarantee a reasonable worst-case assumption, the relevant (conservative) equations were modified.

For the different exposure routes (inhalation and dermal), it is assumed that 70 % of the total amount of substance is available for uptake via skin and 30 % of DMF is released to air. These assumptions are based on the findings by Zuther (2011). In the respective publication, Zuther determined that 70 to 100 % of DMF migrated into a perspiration solution depending on the DMF concentration in the article. The equation for inhalation exposure was further refined by applying reduction factors (i.e. Local Exhaust Ventilation) to account for industrial and/or professional settings. Consecutively, this approach is considered as reasonable worst-case estimating valid exposure values.

Furthermore, it was shown in a quantitative approach that **acrylic fibres** with a DMF concentration of < 1.5 % w/w bear an acceptable risk for industrial workers if specific technical measures are implemented. As indicated in the subsection above for the assessment of PU coated gloves, the usage of "simple" algorithms can often lead to an overestimation of the exposure dose. For the assessment of acrylic fibres, the algorithms have also been modified in order to better account for real workplace situations.

Specific input parameters used for the modelling approach such as "dermal transfer rate" and "amount of substance released to air" could only be estimated due to a lack of scientifically justified information. Nevertheless, estimating these input parameters followed a reasonable worst-case approach.

Reliability of measured data

Referring to the MEGA evaluations by IFA (2012), exposure data are summarized for the whole textile industry. Further subdivisions of data into certain work areas were only performed for "spinning, weaving" and "finishing". Data division for other work areas (i.e. dyeing procedures) or even certain applications are not contained in the document. Consecutively, exposure data cannot be associated with the relevant work place. In addition, sampling of the respective data took place between 2000 and 2011 but exposure values were not correlated to the date of sampling. Thus, a temporal resolution of the measured data cannot be indicated. The above mentioned criteria lead to limited data validity/reliability. Only the exposure duration was considered as relevant by IFA (2012) for a division of DMF exposure values. As final result, the evaluation of the current exposure in a specific work area (here: post-processing of finished acrylic fibres) is not adequate. Further information on the reliability of the MEGA evaluations can be gained in section B.9.4 of this document.
It is assumed that DMF concentrations have been lowered within the last 10 years due to improved technical measures. The MEGA evaluations (IFA, 2012) additionally showed that most of the measured DMF concentrations were below the limit value of 15 mg/m³. However, no relation to any technical measure was drawn which is expected to have a significant impact on the measured DMF concentrations.

Articles which are used by consumers

The performed exposure calculations for consumers show that a DMF concentration of 0.1 % w/w in articles such as **football boots** and **gloves** is of acceptable risk for adult consumers. An increased concentration of DMF residues leads to an unacceptable risk for human health. This further confirms the conclusions drawn for the industrial use of DMF containing articles. However, articles which are used by children (**football boots**; **slimy toys**) bear a potential risk for human health even at a DMF concentration of 0.1 % w/w.

Reliability of the model and validity of estimated exposure values

Referring to the calculations performed by ECETOC TRA v3, predefined use patterns were applied to estimate exposure for consumers due to the usage of sports boots. In order to estimate exposure of children, the relevant parameters for adults were replaced by default values for children (i.e. bodyweight, specific skin surface area). In case of exposure due to the usage of gloves, the use pattern was manually defined by taking realistic conditions of use into account.

According to ECHA REACH Guidance R.15 (Consumer Exposure Estimation, October 2012), ECETOC TRA v3 for consumers combines the conservatism of a first Tier assessment tool with the expert knowledge documented in the ConsExpo fact sheets. The tool aims to balance the Tier 1 assumptions and the generic applicability to a wide range of product categories in order to deliver reasonably plausible outcomes. Conclusively, this approach describes reasonable worst-case scenarios. In this case, exposure estimations are rather overestimated due to the conservative assumption for the dermal transfer factor which was set to 1 (100 % absorption). Exposure values are, however, considered as reliable and valid. Consumer's behaviour cannot be exactly predicted and use conditions might slightly differ which justifies a dermal transfer factor of 1. By this conservative assumption, underestimation of exposure is most unlikely.

With regard to the calculations undertaken for the usage of slimy toys, ConsExpo v5.0 has been used to estimate exposure for children. The software tool is well-know for performing consumer exposure assessments. For each exposure route the complexity (tier) of the model can be selected. Referring to the performed calculations, rather low tier estimates were conducted. According to ECHA REACH Guidance R.15 (October 2012), the applied models for the inhalation and dermal exposure route (inhalation: instantaneous release; dermal: instant application) describe low tier estimates. This approach guarantees a reasonable worst-case.

B. 9.4 Analysis of DMF detections in industrial facilities (MEGA evaluations) in Germany

B.9.4.1 Introduction

In October 2012 the German Institute for Occupational Safety and Health of the Occupational Safety Insurances (Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung, IFA) has published measurement data on DMF for several industry branches. The report is titled: "MEGA evaluations for the preparation of REACH exposure scenarios for N,N-Dimethylformamide" (in German language; refer to Annex B2 and Annex B3 for original version as well as for English translation of the document).

In Germany, the occupational and accident insurances for the different industry sectors generally conduct preventative detections of dangerous substances in industrial facilities. Major part of the detection results serve as on-site verification of mandatory workplace safety values. Results of the analytical measurements are collected at IFA, summarised in reports and also forwarded to the respective companies. Furthermore advise is offered for the member companies regarding optimisation of risk mitigation measurements. Consecutively, all obtained results and the underlying boundary conditions are implemented in the MEGA database and can be assessed also by the involved compensation insurances.

In the following section (B.9.4.2) background information (e.g. detection procedures) is provided, considering origin and structure of the reported DMF measurements. Consecutively (section B.9.4.3), exemplary statistical evaluations of DMF detections are presented.

Section B.9.4.4 comprises discussion and conclusions, regarding the DMF detections in frame of the

MEGA project. In order to verify the relevance of the DMF data reported in the cited MEGA evaluation, the professional organisation (employers liability insurance association) BG ETEM was contacted. This organisation covers mainly textile, energy and electricity industry branches and provided - based on our discussion - a statement with further annotations and explanations.

B.9.4.2 Description of MEGA evaluation (requirements and procedures)

The measured data for workplace exposure evaluated in the MEGA Evaluation report for DMF have been gathered and documented in accordance with the principles of the measurement system of the German social accident insurance institutions for exposure assessment (MGU formerly BGMG). The quality of the MGU is upheld by a quality management system that in essence satisfies the requirements of the German standard DIN EN ISO 9001. The test laboratories are operated in accordance with the German standard DIN EN ISO 17025 "General requirements for the competence of testing and calibration laboratories".

To measure N,N-Dimethylformamide (CAS 68-12-2) exposure at the workplace, two validated methods for the data period (2000 – 2011) were applied:

- Analytical method (2000 – 2007)
  A defined volume of air is sucked by a suitable pump through a silica gel tube (type ADS). After extraction using alkaline methanol (methanol with 2 % KOH), the qualitative and quantitative determination is performed by gas chromatography using a nitrogen selective detector (NSD). The quantitative determination is performed in accordance with the internal standard method. The limit of quantification for the standard method of MGU was 0.3 mg/m³ for a sample volume of 40 L at that time.
- Analytical method (2007 – 2011)
  A defined volume of air is sucked by a suitable pump through an active coal tube (type B). After extraction using acetone/water in the ratio of 98:2, the qualitative and quantitative determination is performed by gas chromatography using a nitrogen selective detector (NSD). The quantitative determination is performed in accordance with the internal standard method. The limit of quantification for the standard method of MGU amounts to 0.2 mg/m³ for a sample volume of 40 L. Source: MGU-Standard method (2012)

All the surveyed data in the MGU are brought together in the MEGA exposure database (measured data on exposure to hazardous substances at the workplace). The MEGA^{pro} software developed by the IFA (formerly BGIA) makes it possible to statistically analyse the data of the MEGA exposure database on the basis of various selection criteria and evaluation strategies.

B.9.4.3 Statistical evaluation of detected DMF concentrations for different industry branches

The following tables are excerpts from the MEGA Evaluation report for DMF. Column “Frequency < number of values [%]” specifically indicates the number of measured values below the analytical quantification limit (total amount and percentage). Column “≤limit value [%]” further refers to the percentage of measured data, which were below the indicated limit value of 15 mg/m³.

Table B98. DMF measurements in different industry branches; Data period 2000 – 2011, Sampling is representative for exposure duration < 6 hours.

Designation	Number	Numbe	Frequenc	Largest	≤ limit	Concentration [mg/m³]

Branch of industry	of measured data	r of firms	y < number of values [%]	quantifi - cation limit [mg/m³]	value [%]	50 percentile	90 percentile	95 percentile
Dataset No. 8; No limitation	163	61	60 36.8	1.3	88.3	+ 0.8	16	32
Dataset No. 61; Plastics industry, rubber industry	28	15	6 21.4	0.2	92.9	1.2	13	20.2
Dataset No. 74; Plastic foil, synthesis	29	3**	0		72.4	7.5	31.1	34.75
Dataset No. 62; Handling of fluid coating materials	9	1**	1 11.1	0.3	11.1			
Dataset No. 63; Textile industry	51	17	26 51	0.3	100	! a. q.	3.9	4.535
Dataset No. 64; Other branches of industry	46	25	27 58.7	1.3	97.8	! a. q.	4.28	5.95

Table B99. DMF measurements in different industry branches; Data period 2000 – 2011, Sampling is representative for exposure duration < 6 hours.

Designation Branch of industry	Number of measured data	Number of firms	Frequency < number of values [%]	Largest quantifi - cation limit [mg/m³]	≤ limit value [%]	Concentration [mg/m³]		
						50 percentile	90 percentile	95 percentile
Dataset No. 9; No limitations	47	27	21 44.7	2.4	83	+ 1.2	19.27	34.745

Dataset No. 66; Textile industry	12	6	4 33.3	0.3	75	2.6	17.76	22.34
Dataset No. 65; Other branches of industry	35	21	17 48.6	2.4	85.7	+ 0.95	20	38.25

The following abbreviations and indices are used in the evaluation tables:

Frequency < values	Number of measured values below the analytical quantification limit
LV	Limit value
a. q.	Analytical quantification limit (limit of quantification LOQ)
*	If any single values fell below the measurement method's analytical quantification limit (a. q.), half of each value was adopted in the evaluation.
+	The distribution value is below the largest analytical quantification limit in the data set. The quantification limit may deviate from the quantification limit quoted in the introduction, e.g. depending on sampling duration or flow rate.
!	The number of measured values below the analytical quantification limit (a. q.) is greater than the number of measured values represented by this cumulative frequency value. No concentration is therefore given for this cumulative frequency value.
**	There are less than five companies in the data set. The data of less than five companies may probably be not sufficient to represent a complete industry group or range. This statement lies on REACH Guidance on information requirements and chemical safety assessment. Chapter R.14: Occupational exposure estimation. R.14.4.5: Selection and interpretation of measured data, Inhalation data: "It should be noted that data from one company is unlikely to be representative of a whole industry sector."

B.9.4.4 Discussion of MEGA data and conclusions

Based on the request of the Dossier submitter to IFA, regarding the relevance of the reported data, the professional organisation (employer's liability insurance association) BG ETEM provided further annotations and explanations in a statement (see Annex B4).

This organisation covers mainly textile, energy and electricity industry branches. Just as insurances for other industry sectors, BG ETEM generally conducts preventative detections of dangerous substances

in industrial facilities. Major part of the measures serves as on-site verification of mandatory workplace safety values. Results of the analytical measurements are summarised in a report and forwarded to the respective company; furthermore advise is offered for the member companies regarding optimisation of risk mitigation measurements. Consecutively, all obtained results and the underlying boundary conditions are implemented in the MEGA database and can by assessed also by the involved compensation insurances.

In the following, as example, the origin of one single workplace measurement (task 10-0975/2007) is clarified in the cited statement by BG ETEM. As indicated in the statistical evaluations for work area groups (IFA, 2012), 92.3 % of the measured values for data set number 67 (Spinning, weaving, wet spinning) were below the limit value of 15 mg/m³. Due to the given number of measured data (13 in total) for this data set, it was concluded that only one workplace measurement was above the limit value. Referring to this data point, BG ETEM gave the following statement:

The substance DMF was detected in a wet-spinning facility for production of polynitrile fibres in the year 2008. This detection was performed in a research institute (member of BG ETEM) and not at a normal manufacturing site. The fibre production arrangement was exclusively build for experimental purposes. Exposition of the operating employee was detected (equipment carried personally by this person), additional stationary measures were also performed closely near and between the baths (i.e. source of emissions). Whereas the detection of the direct personal exposure of the employee revealed a low DMF concentration in air of 5.0 mg/m³, the DMF level above the precipitation bath (32 mg DMF/m³) exceeded the trigger value of 30 mg/m³ (mandatory at that time). DMF concentration between the bath containers amounts to 3 mg/m³.

Conclusion

Based on the explanations mentioned by BG ETEM, it can be concluded that a part of the analytical measurements are not directly related to real workplaces; for instance the detection above a precipitation bath for data set number 67 (Spinning, weaving, wet spinning) lacks any relevance regarding realistic worker exposure. The spatial heterogenity of the survey points clearly limits the significance and validity of the measured values reported in the tables of the IFA MEGA document for DMF. Due to the lack of direct relations between the measured data and workplaces with specified (relevant) activities, exact conclusions on relevant occupational exposures cannot be drawn. Apparently, several DMF-detections were only performed due to technical or scientific considerations and are not connected to direct or even indirect exposure of industrial workers.

B.10 Summary on hazard and risk

B.10.1 Hazard

The information is adopted from the registration dossier, OECD SIDS report (2004) on DMF and literature studies.

N,N-dimethylformamide (DMF) is of low acute toxicity in mammals: LD50 rat (oral) 3040 mg/kg bw, LC50 rat (inhalative, 4 h) > 5900 mg/m³, LD50 rat (dermal) > 3160 mg/kg bw. Main symptoms following exposure were apathy and staggering (oral) and irregular or intermittent respiration (inhalation). It was irritating to the eyes of rabbits but not irritating to the skin of rabbits and rats.

DMF did not show a sensitizing potential when used as a vehicle in a local lymph node assay. In repeated-dose toxicity studies in rats and mice with chronic exposure over 2 years (rats) or 18 months (mice) and subchronic exposure over 13 weeks by inhalation, or in rats treated by oral administration of DMF (90 day feeding study or administration by gavage for 28 days), the predominant target organ was the liver (NOAEC: chronic inhalation rat: 25 ppm (about 80 mg/m³), LOAEC: chronic inhalation mouse: 25 ppm (about 80 mg/m³); NOAEC: subchronic inhalation rat: 100 ppm, mouse: 400 ppm (about 300 mg/m³ and 1210 mg/m³ , respectively); NOAEL: rat, 90 days 200 ppm (about 12 mg/kg bw/day), 28 days about 238 mg/kg bw/day). In a 13-week inhalation study with a limited number of Cynomolgus monkeys no treatment-related effects occurred (NOAEC: 500 ppm (about 1500 mg/m³)).

DMF does not induce chromosome aberrations or gene mutations in various test systems in vivo and in vitro . In addition, no increased tumor incidence was found in carcinogenicity studies in rats and mice that were exposed to 25, 100 and 400 ppm DMF (about 80, 300, and 1210 mg/m³) by inhalation for 2 years or 18 months, respectively.

Reproductive toxicity was observed at the presence of some general toxicity in a continuous breeding study in mice, when DMF was administered orally in the drinking water at doses of 1000, 4000 and 7000 ppm (about 219, 820 and 1455 mg/kg bw/day). The maximal tolerated dose for generalized toxicity was 1000 ppm (about 219 mg/kg bw/day) for the F0 and the F1 generation, thus a systemic NOAEL could not be determined. Significant reproductive toxicity (e.g. reduced fertility and fecundity characterized by reduced pregnancy and mating index (the latter one only in the high dose group), reduced number of litters, reduced average litter size and for the F1 parental males by effects on prostate weight and epididymal spermatozoa concentration, the latter finding only in the high dose group) and developmental toxicity (e.g. reduced survival and growth of pups, increase in craniofacial and sternebral malformations) occurred at 4000 ppm and above. At 1000 ppm, reduced pup weights were found in F2 pups. Thus 1000 ppm (about 219 mg/kg bw/day) was the NOAEL for reproductive and developmental toxicity in F0 and F1, and the LOAEL for developmental toxicity in F2.

Developmental toxicity and teratogenicity occurred in rats and rabbits in various studies (inhalation, oral- or dermal administration) and in mice (oral administration). In rats embryo- /fetotoxicity and teratogenicity were mostly seen at maternally toxic doses, whereas in mice and in rabbits embryo-/fetotoxicity and teratogenicity occurred also at dose levels without maternal toxicity. However, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF.

Rabbit: NOAEC (inhalative) maternal toxicity and teratogenicity as well as embryo-/fetotoxicity 50 ppm (about 150 mg/m³); NOAEL (oral, gavage) maternal toxicity and embryo-/fetotoxicity 65 mg/kg bw/day, teratogenicity 44.1 mg/kg bw/day; NOAEL (dermal) maternal toxicity and teratogenicity as well as embryo-/fetotoxicity 200 mg/kg bw/day).

DMF was studied for its carcinogenicity potential in three inhalation studies, which provides contraversial results for this endpoint. No increased incidence of hepatic tumors occurred in the 2-year

inhalation study in rats and mice, while during another 2 year-inhalation study to DMF vapour increased incidences of benign and malignant neoplasms in two rodent species, hepatocellular adenomas and carcinomas in F344 rats and hepatocellular adenomas and carcinomas and hepatoblastomas in BDF1 mice were observed. A critical evaluation of the manuscripts revealed that technical aspects of two carcinogenicity studies substantially deviated from the OECD 451 guideline. The doses selected exceeded the maximum tolerated dose (MTD), which was exacerbated by probable exposure to an aerosol during atmosphere generation. In addition, the selected animal species (F344 rats) were more sensitive to DMF and therefore may have contributed to increased tumor incidence observed. In humans, case reports of testicular cancer in aircraft repair and leather tannery facilities failed to be confirmed in further studies. Reports of DNA and chromosomal damage in peripheral lymphocytes of subjects exposed to DMF either failed to take into account smoking as a confounder or coexposure to other chemicals.

Regarding ADME parameters, DMF is absorbed via all exposure routes in animals and in humans. In humans, after high exposures (up to 60 ppm) headaches, abdominal pain, nausea, vomiting, dizziness, elevated liver enzymes, and alcohol intolerance (facial flashing and palpitations) were seen. With respect to the metabolism of DMF the following conclusion can be drawn: N-hydroxymethyl-N-methylformamide is the main urinary metabolite and to a minor extent, but with greater toxicological relevance the metabolite mono- N-methylformamide (MMF) occurs which may partially be conjugated to glutathione forming Smethylcarbamoylglutathione. The GSH and its sequel adducts (S-methyl-carbamoylcystein and the corresponding mercapturic acid S-methylcarbamoyl- N-acetyl-cysteine) seem to be responsible for developmental toxic effects. At higher doses, DMF inhibits its own metabolism, i.e. the formyloxidation to MMF which precedes the GSH binding.

Persons who repeatedly inhaled DMF excreted the mercapturic acid at levels of ~ 13% of the dose with a total half-life (i.e. DMF biotransformation and excretion) of 23 hours. Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Furthermore, ethanol induces cytochrome P450 2E1 which facilitates the initial hydroxylation of DMF. Thus, exposure to DMF can cause severe alcohol intolerance.

B.10.2 Risk

Regarding REACH requirements, the substance DMF was registered in 2010. The Identified Uses mentioned in the registration dossier at that time were updated in February 2014. As a consequence, the whole risk assessment was sufficiently revised in the CSR. This comprised the inclusion of exposure scenarios, additional exposure calculations for specific applications and a separate TIER 2 assessment which was based on measured data.

Tiered approach for risk assessment

In order to achieve an adequate refinement of the risk assessment - in frame of a tiered approach - all identified Downstream Users of the Lead Registrant were requested to provide specific information regarding their use patterns of the substance. For this purpose, two consecutive questionnaires were provided to the Downstream Users. In accordance with the REACH Use Descriptor System, information regarding the relevant Sector of Use (SU), Product Category (PC), Article Category (AC), Process Category (PROC) and Environmental Release Category (ERC) were gained in the first questionnaire. In addition, other important assessment parameters such as tonnages, measured data, Operational Conditions (OCs) and Risk Management Measures (RMMs) for each application/process were requested via a second questionnaire. Due to this detailed and complex approach, exposure estimations and risk characterisations take the current state of the art into account.

After receiving all relevant information, the risk assessment of the substance was revised accordingly in the CSR. The exposure towards DMF at the workplace was assessed in a first step by a TIER 1 (exposure modelling) approach. For this approach, the software tool CHESAR v2.2 was used which implements ECETOC TRA v3.0 for exposure modelling referring to Human Health. Due to the fact that

relevant measured data from several different industrial sites was available, a TIER 2 assessment was additionally elaborated.

Results of risk assessment

According to the TIER 1 approach, exposures resulting from processes under elevated temperatures, processes requiring intensive manual applications and open processes are relatively high which, however, can be addressed by the applied RMMs and OCs. In general, the estimated exposure levels ranged from 0.023 to 3.046 mg/m³ for the inhalation exposure (systemic, long-term). Calculated dermal exposure ranged from 0.007 to 2.7 mg/kg bw/day (systemic, long-term).

The highest exposure levels were estimated for specific processes (PROC 10 – Roller application or brushing; PROC 19 – Hand mixing with intimate contact and only PPE available) which are considered to bear a potential risk towards Human Health. Inhalation exposure was estimated up to 4.568 mg/m³ (systemic, long-term) while dermal exposure was estimated to amount up to 7.072 mg/kg bw/day (systemic, long-term) for these process categories.

By combining the derived DNELs with the exposure estimates, risk characterisation ratios (RCRs) were obtained. Combined RCRs above the trigger values of 1.0 were only calculated for PROC 10 and PROC 19 identifying a potential risk. The fact that RCRs for inhalation are well below 1.0 for most of the industrial applications was further confirmed by the TIER 2 assessment. Within the TIER 2 approach, all measured data values were below the OEL value of 15 mg/m³. Measured data for PROC 10 and PROC 19 were not available. It is therefore concluded that risks are not sufficiently controlled for the indicated specific processes. It was also shown that applied RMMs and/or OCs for these processes cannot decrease exposure to an adequate level.

Article assessment

Furthermore and in addition to the original registration dossier, an assessment of selected articles (e.g. gloves or sport shoes) was performed since analytical detections in the past revealed considerable DMF residues, especially in no-name products imported from Asia. Considering DMF levels of 0.1 %, 0.3 % and 1.5 %, critical levels could be identified for the different articles, in use by industrial and professional workers as well as by the general public (consumers). A trigger value of RCR ≤ 1 was used for this assessment. All in all, different modelling approaches were applied.

Relevant modelling approaches and the final results of this assessment are briefly summarized as follows:

<u>Industrial use</u>

- Gloves containing 0.1 % w/w DMF residues were estimated to bear an acceptable risk for Human Health. Calculation was based on algorithms which have been slightly modified.

- Usage of acrylic fibres containing 1.5 % w/w DMF residues also resulted in an acceptable risk. Calculation was based on algorithms which have been slightly modified.

<u>Consumer use</u>

- Sports shoes used by adults with a DMF content of 0.1 % w/w do not bear a potential risk towards Human Health. The assessment is based on exposure modelling using ECETOC TRA v3.0.

- Sports shoes used by children with a DMF content of 0.1 % w/w do bear a potential risk towards Human Health. The assessment is also based on the usage of ECETOC TRA v3.0 as modelling tool.

- Gloves containing 0.1 % w/w DMF residues were estimated to bear an acceptable risk for Human

Health. Calculation was based on ECETOC TRA v3.0.

- This modelling approach by using ConsExpo v5.0 definitely showed that DMF residues of 0.1 % w/w are not of acceptable risk for consumers (subpopulation: toddlers).

MEGA evaluation for DMF at industrial sites in Germany

In the closing section (B.9.4), results of analytical DMF measurements at industrial sites in Germany were presented. The data was gathered by the German Institute for Occupational Safety and Health of the Occupational Safety Insurances (IFA) and consists of DMF detections in several industry branches (e.g. textile industry). However, most of the detection results cannot be directly interpreted as relevant regarding worker exposure in the production facilities. This is due to the fact that part of measurements were undertaken for scientific or technical purposes and the outcome is not relevant for assessment of realistic employee exposure towards DMF under typical production conditions. Unfortunately, such detection results are not separately reported by IFA, but mixed with occupational health data.

Part C. Available information on alternatives

Within this chapter, the various applications of DMF are described, outlining the advantages of DMF and to which extent suitable alternatives are available and / or already research was done in order to identify those. Unfortunately, this information is generally rather limited due to its nature. Any research regarding process optimisation and the outcoming results are generally not published. Either, because this is considered as confidential business information, or because no positive results could be obtained. Hence, this chapter can only present a limited amount of citable literature sources ; a large amount of information was obtained during stakeholder consultations.

C.1 Identification of potential alternative substances and techniques

DMF is one of a class of extremely useful solvents designated as polar aprotics. The physical properties of these solvents make them an attractive choice from a chemistry perspective in the synthesis of active intermediates for pharmaceuticals and veterinary medicines. A dipolar aprotic solvent has a comparatively high relative permittivity (or dielectric constant), greater than ca. 15, and a sizable permanent dipole moment, that cannot donate suitably labile hydrogen atoms to form strong hydrogen bonds, e.g. dimethyl sulfoxide (PAC, 1994). In other words, polar aprotics all have the advantage of being able to dissolve a wide range of substances, but do not have the acidic proton that most highly polar solvents have. For many reactions, the acidic proton can lead to complications in the reactions. Thus, as industrial solvents they are ideal for certain reaction types. DMF, often called a 'universal solvent,' offers sufficient solubility of many inorganic reagents (it is not only completely miscible with water, but also solves e.g. salts, acids & bases) that facilitates chemical reactions that would not be feasible or robust in many other organic solvents. In some cases, the properties of DMF are unique in effecting a desired reaction reactivity, selectivity, solubility, or purification. Hence, the availability of technical feasible alternatives will differ per use application.

DMF offers many advantages which include i.a.:

- High solubility of many active pharmaceutical ingredients (APIs) and intermediates, which often have very poor solubility in less polar solvents. This facilitates processes that require minimal solvent quantities, compared with the much larger volumes of other solvents that may be required.
- Sufficient solubility of many inorganic reagents (e.g. acids & bases) that facilitates chemical reactions that would not be practicable or robust in many other organic solvents.
- Reaction rates of certain reactions (e.g. nucleophilic substitution) are substantially enhanced due to the solvent polarity. Polar aprotic solvents such as DMF are essential for these reactions, since they prevent unreacted materials from being carried forward in the process stream, minimize the formation of side products, and produce intermediates and API of the highest quality.
- The use of these solvents can be essential (due to their relatively low acidity) when strong bases are employed as these materials would be completely consumed by side reactions if protic solvents were used.
- Water miscibility – for example facilitating precipitation, and subsequent isolation, of products from reaction liquors through the addition of water as an anti-solvent.
- A high boiling point (153°C) – allowing reactions to be carried out at much higher temperatures than would be achievable in many organic solvents, without the need to operate under pressure (often not operationally feasible in typical pharmaceutical reactors, and inherently of greater operational hazard). An additional benefit is that the potential for solvent emissions associated with processing is less than those associated with many other solvents.

DMF is therefore used as a solvent within research and development laboratories, development manufacturing pilot plants and commercial manufacturing plants for manufacturing active ingredients for pharmaceuticals and veterinary medicines.

The use of DMF in electronics, mainly in the manufacture of printed circuit boards, is a large market in Asia. DMF is also widely used as a reagent and catalyst for syntheses in organic chemistry. The pharmaceutical industry uses DMF as solvent in syntheses and for crystallizing. Another use is for selective absorption e.g. extraction of acetylene in ethene streams, butadiene from mixed C4-streams (butane, iso-butane, butene and butadiene) or aromatic hydrocarbons from aliphatic hydrocarbons in the petrochemical industry. DMF is also used for storage of acetylene in gas cylinders for safety reasons. But in this use it is practically waiting to be burnt completely at >1000°C with the acetylene during welding. DMF can also be used in the manufacturing of electrical allocation equipment and circuitry metal industry.

As a solvent used in synthesis, DMF is not supposed to be a component of the final product although some traces may still remain. Consequently, DMF in articles for example from the textile or plastic industry cannot entirely be excluded, in particular if the articles are produced outside of EU-countries and being imported into the EU.

General concern was raised with regard to “green chemistry”. Especially the pharmaceutical industry is playing an active role in the development of green chemistry. Kerton describes three categories of solvents: Preferred, useable and undesirable (Kerton, 2009). The former includes e.g. water, acetone or ethanol, usable are e.g. cyclohexane, toluene or DMSO. Undesirable however are e.g. pentane, hexane(s), DMF, NMP, acetonitrile, THF, chloroform, dioxane, DME, carbon tetrachloride or benzene. The solvents in this category are there for a number of reasons: pentane and diethyl ether because of their low flash points; the chlorinated solvents, pyridine and benzene because they are carcinogens; and the polar aprotic solvents N,N-dimethylformamide (DMF) and N-methyl pyrolidin-2-one (NMP) because they are toxic. Alternatives for many of the former classes of solvents are readily available in most laboratories. Unfortunately, no truly suitable alternatives to DMF, NMP and DMA are available at this time. Acetonitrile can be used in some cases but is not an ideal replacement (Kerton, 2009).

Based on previous evaluation by the Agency (ECHA, 2013), DMF is used mainly:

- as solvent in synthesis of chemicals (e.g. Active Pharmaceutical ingredients (API), crop protection ingredients) (~ 50%),
- as solvent in the production of polyurethane coated textiles such as artificial leather, rain and protection wear, footwear, medical mattress covers, surgical incise films etc. (~25%)
- as solvent in the production of synthetic fibers (~10%),
- in other applications such as in the electronic industry, in formulation of mixtures, as gas stabiliser in acetylene cylinders, in the production of medical devices (e.g. In Vitro Diagnostic Devices (IVD)), as cleaning solvent, as intermediate, as laboratory chemical etc.

So, the use of alternatives may not be feasible in many cases because of their toxicological characteristics (e.g. classification as a carcinogen) or because of technical or economic considerations. This will be outlined in detail below.

C.1.1 Generic uses

C.1.1.1 Solvent in the manufacture of substances

Generally, it should be noted that within this chapter only general descriptions can be made as the specific reaction conditions are strongly dependent on the desired product. However, these generic descriptions will be underlined the some illustrative examples. Also, it should be regarded that several applications are specifically protected by companies’ patents. Changing the synthesis conditions would hence not only have negative impact on the performance or general feasibility of a process, but could also invalidate those patents, clearly resulting in further negative economic impact on companies

business, as will be outlined further in chapter F, socioeconomic analysis.

C.1.1.1.1 Solvent in SN reactions

DMF is widely used as solvent in the synthesis of chemicals, especially involving SN2 and SNAr reactions. Aprotic solvents are frequently used for SN2 displacement reactions, where they stabilize the charge-separation that occurs in the transition state (Hultin, 2002). In SN2 reactions, both the nucleophilicity as well as the facilitation of the elimination of the nucleophilic leaving group are relevant for the determination of the rate of the reaction. Aprotic solvents generally solve cations, not the anions, i.e. the nucleophiles, which are hence not hindered by a solvent shell, whereas the solvation of the former supports the elimination step. DMF solves the cation with its free electron pairs on the oxygen and nitrogen atom and efficiently blocks the cation from the anion due to its size. Whereas polar, protic solvents are preferred in SN1 reactions as they are able to solve both the resulting cation and anion, SN2 reactions prefer i.a. polar-aprotic solvents that do not solvate the nucleophile.

Generally, nucleophiles are more reactive in aprotic than protic solvents, and are commonly used when polar protic solvents give poor results. Hence, the group of polar aprotic solvents can generally not be replaced by other solvent types.

DMF behaves in many ways like DMSO, but it is not significantly nucleophilic. It is also very high boiling, but since its freezing point is –60 °C, it can be used at lower temperatures than can DMSO (melting point of 18.5°C). DMSO is a good solvent for SN2 displacements, but is incompatible with very strong nucleophiles or bases (Hultin, 2002) as well as not suitable for reactions at low temperatures due to its rather high melting point of 18°C. Also its high boiling point poses a big drawback because it is quite difficult to be removed by evaporation.

Other alternatives, such as acetone, cannot replace DMF in many application either. Because the ketone group is moderately electrophilic, acetone cannot be used in reactions involving very strong nucleophiles such as carbanions or Grignard reagents. These reagents are also very strong bases, and will deprotonate acetone to form an enolate ion (Hultin, 2002).

The solvent plays an important role in the kinetic of a SN2 reaction. For example, the reaction of an acetate ion with iodomethane to methyl acetate according to a SN2 mechanism occurs 10 x 10^6 faster in DMF than in methanol. The influence of the solvent on the reaction rate is not only dependent on e.g. the polarity, i.e. for example measured as the dielectric coefficient, as polar solvents lower the interactions of the solved ions, but in general in the way they modify the activation energy ΔG of a reaction. As an example, despite the fact that DMF and methanol as an protic polar solvent have nearly similar dielectric coefficients, the reaction rate constants are different. Table C1 shows the free energy of the reactions of several nucleophils in DMF and methanol (Streitwieser, 1994):

Table C1. Free activation energies for the reaction of various nucleophiles with iodomethane at 25°C in DMF and methanol, according to Streitwieser, 1994.

Nucleophile \ Solvent	DMF	CH_3OH
CN^-	14.0	21.8
$CH_3CO_2^-$	15.7	25.1
NO_2^-	16.8	22.5
N_3^-	16.8	23.0
Cl^-	16.9	25.0
Br^-	17.3	23.0
SCN^-	19.0	22.0
I^-	20.9	18.0
$(CH_3)_2S$	21.8	23.6

Basically one can say that protic solvents such as ethanol or methanol slow down SN2 reactions by solvation of the reacting nucleophile and hence “isolating” it from their reaction partner, they lower the ground state energy of the nucleophile. Polar aprotic solvents, on the other hand, raise the ground state

energy of the nucleophile (McMurry, 2010) and hence force it into reaction. Table C2 illustrates the relative reactivity via the reaction rate of azide ion with 1-bromobutane in different solvents:

Table C2. Relative reactivity of azide ion with 1-bromobutane in different solvents, according to McMurry, 2010.

Solvent	Protic polar solvents		Aprotic polar solvents			
	CH_3OH	H_2O	DMSO	DMF	CH_3CN	$((CH_3)_2N)PO$ (HMPA)
Relative reactivity	1	7	1,300	2,800	5,000	200,000

In consequence, only aprotic polar solvents may serve as possible alternatives for DMF, and even the use of those may bear problems due to possibly required reaction rates, e.g. taking into account possible endothermic reactions. Also, as already mentioned, some of them are similarly classified like DMF.

DMSO may be taken into account due to its minor hazard, but in this case several different problems were noted: 1st the yield of the process drastically decreases; 2nd this solvent reacts with some impurities to generate various sulfides; 3rd the melting point is much higher than that of DMF and this generate problems to the plant (particularly in winter) (ECHA, 2012).

C.1.1.1.2 Fine Chemicals

In biochemistry, DMF is e.g. used for the coupling of amino acids during the peptide synthesis (Khattab, 2001). Peptide solid phase synthesis involves coupling and deprotection steps with protection groups. Bacsa et al. use e.g. 30% piperidine in DMF which was used in a two-step cleavage protocol (Bacsa, 2010).

Other methods using DMF as solvent, e.g. applied in amide bond formation during peptide synthesis, also underlie an SN2 reaction, for example the synthesis of N-Carboxy anhydrides or Leuch's anhydrides. Cyclic anhydrides can be readily prepared from unprotected amino acids and phosgene. An alternative procedure consists of reacting N-protected (Boc, Cbz, Fmoc) amino acids with thionyl chloride and DMF (Montalbetti, 2005).

DMF is widely used in the synthesis of fine chemicals. Besides its role as solvent in SN2 reactions as described above, DMF can also be applied as catalyst, e.g. in Acyl chloride formation. Thionyl chloride $SOCl_2$, oxalyl chloride $(COCl)_2$, phosphorus trichloride PCl_3, phosphorus oxychloride $POCl_3$ and phosphorus pentachloride PCl_5 are commonly used to generate acyl chlorides from their corresponding acids. These reactions are often promoted by the addition of a drop of dimethylformamide (DMF), as depicted in the following scheme of the catalytic cycle of the activator DMF (Montalbetti, 2005).

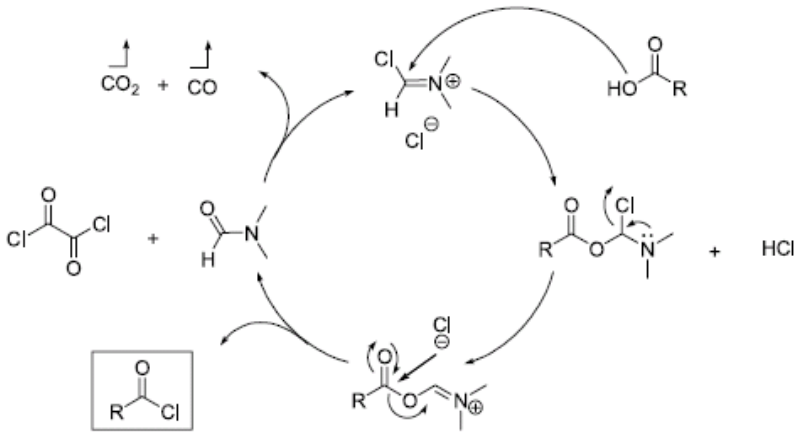


Figure C1: Activation with DMF: catalytic cycle, taken from Montalbetti, 2005.

As it was shown, DMF is used in very specific applications. The synthesis of a specific product may only be successful applying exactly the respective reaction parameters and may not allow any modification, including the application of DMF. Also here, dependent on the specific use, DMF cannot be replaced globally.

C.1.1.1.3 Pharmaceuticals

Besides the generally applicable principles in organic chemistry synthesis, specific circumstances need to be taken into account when regarding pharmaceuticals. Pharmaceuticals, Active Pharmaceutical Ingredients (APIs), must be manufactured according to the principles of Good Manufacturing Practice (GMP). According to Directive 2003/94/EC, "*for medicinal products, any new manufacture or important modification of a manufacturing process of a medicinal product shall be validated. Critical phases of manufacturing processes shall be regularly re-validated.*" The DG Enterprise and Industry specifies more concretely: "*Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organisational units, and reviewed and approved by the quality unit(s).*" and "*The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.*" (EC, 2010).

Taking into consideration the marketing of APIs, which is granted by the European Medicines Agency (EMA) only when production is executed according to the principles described in the authorization, one realizes the enormous interferences, which would arise. Any substitution of DMF (performed on a case-by-case basis - if possible at all) would trigger re-validation and re-registration of each product affected, as set out more precisely in Regulation (EC) No 1234/2008 and related documents, causing high costs and requiring additional animal and human testing. Developing, evaluating, validating a new process step in an existing process used for manufacturing an Active Pharmaceutical Ingredient is very time-consuming and costly. New impurities, possibly resulting from the usage of the new solvent, must be checked for, identified, analysed, removed, etc. and the final impurity profile of the drug substance, i.e. the quality of the drug must be defined. This implies that the new drug's safety has to be re-established and approved by the EMA; this may imply substantial safety testing, and will require updates or new submissions of the regulatory dossier in all countries where the drug is on the market. In consequence, modification of the applied solvent triggers a long technical and regulatory changeover time, which could also lead a critical undersupply of essential pharmaceutical products.

Rates and selectivity of certain reactions (e.g. nucleophilic substitutions) are substantially enhanced due to the solvent polarity and other properties. This prevents unreacted materials from being carried forward in the process stream, minimizes the formation of side products, and produces intermediates and APIs of the highest quality. DMF, often called a 'universal solvent', offers sufficient solubility of many inorganic reagents (e.g. salts, acids and bases) that facilitates chemical reactions that would not be feasible or robust in many other organic solvents. In some cases, the properties of DMF are unique in effecting a desired reaction reactivity, selectivity, solubility, or purification. No comparable performance with any other solvent is known (APIs often have a poor solubility in less polar solvents) or the alternative solvents pose a greater environmental, occupational health, or other concern. The most common "direct" alternatives are DMAC or NMP. Others include formamide (CAS 75-12-7), N-methylacetamide (CAS 79-16-3) and Hexamethylphosphoric triamide, (CAS 680-31-9). However, these alternatives also carry essentially the same health hazard as DMF. Moreover some of above mentioned substance also exhibit acute toxic effect to humans. DMSO might be an alternative based in some criteria, but actually is not suitable because of its high melting point and commonly known and reported problems with stability (e.g. potentially generating new/unknown impurities). Acetonitrile might be a potential substitute, but this substance has a much lower solvating power, which would decrease the yield of the chemical reaction, and increase costs, amount of waste, energy use, and so on.

Many uses of DMF are critical for the manufacture of fine chemicals that are used by the Pharmaceutical and Biopharmaceutical industries to manufacture and purify Active Pharmaceutical

Ingredients. N,N-dimethylformamide is used under controlled conditions in mainly closed systems as process chemical (solvent) and thus N,N-dimethylformamide is not part of the final fine chemicals. There are currently no known technically equivalent substitutes for many uses. The Pharmaceutical and Biopharmaceutical industries use the final fine chemicals, which are not medicinal products, to finally synthesize medicinal products such as antisense oligonucleotides. The fine chemicals are used for the synthesis of therapeutic oligonucleotides such as DNA, RNA, modified Oligodesoxynucleotides (ODN) or mixed chimeric ODN. These biomolecules are used in the therapeutic treatment of several diseases such as Huntington disease, cancers (including lung cancer, colorectal carcinoma, pancreatic carcinoma, malignant glioma and malignant melanoma), diabetes, Amyotrophic Lateral Sclerosis (ALS), Duchenne muscular dystrophy and diseases such as Asthma, Arthritis and Pouchitis with an inflammatory component. One antisense drug, Fomivirsen (marketed as Vitravene), has been approved by the U.S. Food and Drug Administration (FDA) as a treatment for Cytomegalovirus Retinitis. The inability to use N,N-dimethylformamide or introduce less hazardous alternatives in the manufacturing processes of fine chemicals used by the Pharmaceutical and Biopharmaceutical industries will adversely impact the production of Active Pharmaceutical Ingredients and medicinal products (ECHA, 2012).

By definition, the IVD industry and other sectors which rely on biotechnology for their manufacturing process will use a large number of biologically active substances. In other words, the substances used in IVDs often rely for their fundamental function on chemical characteristics that are at the same time the reason for their classification as CMR and/or PBT/vPvB. Therefore often the only possible substitute – where an alternative is in fact possible – will be a substance with similar intrinsic properties. Moreover, without sufficient testing, the substitution bears the risk for false negative or false positive tests, which has tremendous and possibly fatal consequences for patients and the health of the population. The cost and resources needed for re-validating/verifying hundreds of IVDs manufactured in Europe due to the use of relatively small quantities of DMF – for which the only substitute would be another polar aprotic solvent – seems indeed disproportionate to the intended policy outcome which is to manage the exposure risk to worker health and safety.

It also should be mentioned that Pharmaceuticals have their own limits for residual solvents (<0.08% for DMF). This is below the limit of 0.1% generally applied for SVHC.

C.1.1.1.4 Plant Protection Products

Similarly to active pharmaceutical ingredients, the approval of a plant protection product (PPP) "may be subject to conditions and restrictions including: a) the minimum degree of purity of the active substance; (b) the nature and maximum content of certain impurities" according to Regulation (EC) No 1107/2009. An application for the approval must be submitted for both an active substance and an amendment to the conditions of an approval. Hence, if the impurity profile for a PPP changes the PPP Regulation 1107/2009, new registrations are required. This means that a lot of new studies have to be performed and registrations in every country, for every formulation and every crop have to be resubmitted. This is very costly work and will not be feasible. Furthermore a lot of the required studies involve animals and this will go against one of the key principles in REACH; to reduce testing on vertebrate animals.

Also for the synthesis of PPPs, the conditions including solvents are individual and tailor-made for the respective product. Regarding for example flavones and alkaloids, which contain the methylenedioxy-1,2-benzene group (also known as benzo[1,3]dioxole) are biologically active and have found extensive application in perfumery and in the manufacture of favours and insecticides. Particularly interesting are the benzo[1,3]dioxoles substituted in position 5 with an alkyl group, which can be found i.a. in sassafras oil, since they may be used as key reagents in the synthesis of the aforementioned products of industrial importance as well as of other products, such as piperonyl butoxide, an active ingredient exhibiting insecticide action. Therefore, the need for effective processes for the synthesis of 5-allylbenzo[1,3]dioxoles is deeply felt. Borzatta et al. developed an effective synthesis of 5-alkylbenzo[1,3]dioxoles, whereby one essential reaction step involves an aprotic polar solvent, such as DMF, dependent on the specific compound, e.g. 5-propyl benzodioxole, preferably a mixture of DMF and CH2Cl2 (Borzatta, 2001). In the synthesis of insecticidal 1,3-benzodioxol

derivatives, DMF as solvent is necessarily required to avoid beta-elimination under conditions favouring this reaction, e.g. when reacting ethoxyl-arylic compounds in the presence of sodium or potassium hydroxide (Schelling, 1976).

Also in this context, alternative solvents have been evaluated i.a. for the synthesis of an intermediate for the above-mentioned dioxole derivatives. From this investigation results that exists a group of solvent that have a classification similar to that of the DMF (moreover, some of these substances are in the candidate list) and another group of solvent (at the moment not classified hazardous as the DMF) present a cost that is much higher than the solvent in object. In addition, for this last group of solvents some problems were noted: 1st the yield of the step to generate the intermediate drastically decreases; 2nd, as already mentioned in other applications, the solvents react to generate various impurities which drastically reduce the final yield of the final product of synthesis; 3rd the boiling points are so different (higher) than that of DMF that a modification of the plant is necessary to ensure the reliability of the whole process of synthesis. This compound is irreplaceable as there is not another substance like it known. As consequence, stop the placing on the market of this substance for a long period for sure leads to negative consequences for the health of those populations, that due to the climatic conditions in which they live, are obliged to use the insecticides (DMF Consortium, 2014).

The use of DMF as solvent results in a very pure end product without neither impurities nor DMF. Within the conditions described in the literature mentioned above, 26 solvents were investigated in more than 120 experiments with a variation of both the alkali and catalyst. A few aprotic polar solvents were found to be almost comparable with DMF in yield, but they turned out to have similar health hazards or other technical problems as indicated below.

- DMAc (N,N-dimethylacetamide, CAS No: 127-19-5): From a technical point of view DMAc is a suitable solvent but it is classified toxic for reproduction category 1B (1272/2008/CE) like DMF and is already on the Candidate list of Substances of Very High Concern and has been prioritised for REACH Annex XIV inclusion.

- NMP (n-Methylpyrrolidone, CAS No: 872-50-4): From a technical point of view NMP is a suitable solvent but it is classified toxic for reproduction category 1B (1272/2008/CE) like DMF and is already on Annex XVII.

- HMPT (Hexamethylphosphoric triamide, CAS No: 680-31-9): HMPT is classified mutagenic in Cat 1B and carcinogenic in Cat 1B and would therefore not be a suitable substitute.

- Benzene (CAS No: 71-43-2): It is very difficult to remove from the final product. In China it is used in the production and here the evaporation takes place in open systems. Benzene is among others classified mutagenic in Cat 1B and carcinogenic in Cat 1A and would therefore not be a suitable substitute.

- DMSO (dimethyl sulfoxide, CAS No: 67-68-5): From a technical point of view DMSO is a suitable solvent although the yield is lower resulting in a higher use of chemicals and increasing waste streams. As already mentioned, DMSO has a higher melting point (18°C) which requires higher operating temperatures (hence more energy) and a mild corrosive nature (requiring stainless steel equipment). It is difficult to regenerate large quantities of DMSO due to thermal instability and there have been reported accidents in the literature. However, the worst concern is that it is not possible to fully remove DMSO from the end product which is a PPP. This would result in a widespread exposure of DMSO on the crops, environment and man.

C.1.1.2 Solvent for the Petrochemical Industry

C.1.1.2.1 Butadiene production and Extraction solvent

Butadien recovery

DMF is used in extracting butadiene from the C4 distillate obtained by naphtha cracking, etc. and in separating isoprene from C5 distillate. White (White, 2007) describes the produduction of butadiene by four different processes. A summary of the major processes is listed in the table below.

The most applied is a non-aqueous solvent extraction with DMF, followed by the extractive distillation using aqueous N-methyl pyrrolidone (NMP) as a solvent. The other two processes, using acetylene hydrogenation and acetonitrile extraction, are less applied. Other possible solvents to extract butadiene besides DMF are N-methyl pyrrolidone (NMP) and acetonitrile (ACN). Furthermore, the BREF for the large volume organic chemical industry mentions acetone, furfural, acetonitrile (ACN), dimethylacetamide, dimethylformamide, and N-methyl pyrrolidone (NMP) as solvents used for butadiene extraction (EC, 2003).
Obviously, alternative solvents and processes to substitute DMF in butadiene extraction are available. However, many of those solvents bear the same hazardous properties as DMF itself, and in addition, applying alternative production processes might enormously raise the costs associated with butadiene production.

Table C3: Major Butadiene Recovery Processes (ACC, 2010).

Process	**Description (Solvent used)**
Process A	Butadiene Purification via Acetylene Hydrogenation and Extractive Distillation Using Aqueous methoxy-proprio-nitrile (MOPN)/Furfural
Process B	Extractive and Conventional Distillation Process Using Aqueous n-methyl-2-pyrrolidone (NMP)
Process C	Dimethylformamide (DMF) Solvent Extraction Process [nonaqueous]
Process D	Aqueous Separation and Acetonitrile (ACN) Extraction

DMF is used in extracting butadiene from the C4 distillate obtained by naptha cracking, etc. and in separating isoprene from C5 distillate. DMF is also used in extracting solvent of aromatic hydrocarbons in petroleum refining.

The strong selectivity of DMF is used for the manufacture of 1,3-butadiene. Butadiene is the final product of the pyrolysis of a C4-fraction processing by extractive distillation and rectification. Butadiene is used for the production of e-SBR, s-SBR, liquid rubber and ABS resins. The DMF extraction process is licensed by ZEON Industries (GBP process). The principle of the method is the different boiling point of hydrocarbons in DMF (see Table below). The synthesis of 1,3-butadiene starts with a C4-fraction and DMF as solvent. Within usual three steps, 1,3-butadiene is formed and residues (e.g. vinyl acetylene and other acetylenes). By-products are removed using two distillation columns and a pure 1,3-butadiene product stream is produced (ACC, 2010).

Table C4: Boiling Point and Solubility in DMF

Component	**Boiling point (°C)**	**Solubility Vol/Vol/1atm**	**Remark**
Propane	-42	4.0 (25°C)	Less soluble from 1st extractive distillation section
Propylene	-47.7	8.2 (25°C)	
iso-Butane	-11.7	9.2 (20°C)	
Allene	-34.3	40.0 (20°C)	
n-Butane	-0.5	16.5 (20°C)	
iso-Butene	-6.9	28.0 (20°C)	
1-Butene	-6.3	24.6 (20°C)	
t-2-Butene	+0.9	35.5 (20°C)	
c-2-Butene	+3.7	51 (20°C)	
1,3-Butadiene	-4.4	83.4 (20°C)	
Methylacetylene	-23.2	85 (20°C)	More soluble from

Component	Boiling point (°C)	Solubility Vol/Vol/1atm	Remark
1.2-Butadiene	+10.3	160 (20°C)	2nd extractive distillation section
Vinylacetylene	+5.1	350 (20°C)	

The estimated share of DMF as extracting agent for butadiene is about 1%. ZEON's GPB process for butadiene extraction technology, developed through exclusive technology, is licensed to forty nine (49) plants in nineteen (19) countries worldwide. In Europe, currently eight (8) plants are operating. (ZEON, 2014).

Butadiene (Kt)					
	2009	2010	2011	2012	2013
Capacity	2,485	2,490	2,500	2,483	2,518
Production	1,813	2,079	2,087	2,049	1,925

Figure C2: Butadiene production in the EU (Source: Petrochemicals Europe, 2014)

Other Extractions

In addition, DMF is used to recover ethylene, e.g. the Linde Acetylene Recovery Unit (ARU) as well as for the extraction of aromatics from the carbon and for the four fractions separated recovery from butadiene and C5-fraction. DMF is also used for separation of isoprene or paraffin from the non-hydrocarbon components. Due to the good selectivity, DMF is used for separation of acid and terephthalic acid since the solubility of acid dimethyl formamide is greater than the solubility of terephthalic acid. Also, DMF gas can be used as absorbent, used for the separation and purification of gases.

A few applications are described which deal with natural herbal DMF extracts e.g. *Ginkho biloba*. However, this is a minor application and seems not to be used in the EU.

C.1.1.2.2 Transport of Acetylene Gas

Since acetylene is a chemically unstable gas, specific measures for its transport and end use must be adopted. It may only be transported in pressure receptacles of limited size -gas cylinders- filled with a porous mass saturated with a solvent (DMF) that will adsorb the acetylene and stabilizes it. First of all, this is required for safety reasons, as acetylene only in its pure gaseous state is very unstable. Second, by solvation an amount ten times higher per volume unit can be transported compared to the unsolved form, making DMF of utmost importance to reduce transport costs.

Relevant properties to enable the safe and efficient transport of acetylene gas are both the high solubility coefficient of DMF for acetylene and, even more important, the very low vapour pressure of DMF of 3.77 hPa at 20°C. Whereas the former property is mainly relevant for transport efficiency, the latter determines both the safety of handling as well as the purity and hence performance of the acetylene gas. The solvent stays in the gas cylinder, but is carried as impurities when the acetylene is decanted by the customers. Under the high pressure of the transport cylinder, the whole amount of acetylen gas is solved in DMF, and during its application, e.g. welding, the pressure gets continuously reduced, shifting the equilibrium to the gasous form, whereby the free acetylene is used up directly. Due to the very low vapour pressure of DMF, it virtually completely remains in the cylinder. DMF is used in applications where the level of impurities need to be very low (ppm level) for safety and quality reasons, e.g. electronic industry or glass industry. Generally, after complete draining of the gas, there is no need to refill DMF into the transport cylinder, which would be required for other solvents, as it does not

evaporate and hence does not contaminate the acetylene gas (Wolfs, 2014). Only every 10 years each acetylene cylinder is topped up under closed conditions with DMF to compensate for the solvent that has been carried away (and burned) with the acetylene used by the customers (DMF Consortium, 2014). Table C5 gives an overview on already assessed alternatives (Wolfs, 2014) with regard to the above-mentioned required properties:

Table C5: Overview of acetylene solvents as potential substitutes of DMF in interconnected acetylene cylinders (Wolfs, 2014)

	DMF	**NMP**	**DMSO**	**Diglyme**	**HPMA**
	N,N-Dimethyl-formamide	N-Methyl-2-pyrrolidone	Dimethyl-sulfoxide	Diethylene glycol dimethyl ether	Hexametapol hexamethyl-phosphoramide
CAS number	68-12-2	872-50-4	67-68-5	111-96-6	680-31-9
Molecular Weight (g/mol)	73.09	99.13	78.13	134.17	179.2
Boiling Point (°C)	153	202	189	162	232.5
Vapour Pressure (hPa 20°C)	**3.8**	**0.39**	**0.6**	**2.15**	**0.04**
Freezing Point (°C)	**-61**	**-24**	**18.5**	**-68**	**7.2**
CLP classification	**Repr. 1B** Acute Tox. 4 * Acute Tox. 4 * Eye Irrit. 2	**Repr. 1B** Eye Irrit. 2 STOT SE 3 Skin Irrit. 2	Not classified	Flam. Liq. 3 **Repr. 1B**	**Carc. 1B** **Muta. 1B**
Suitability as substitute for DMF	Current solvent in use for special applications of acetylene requiring high purity	No suitable substitute because of CMR classification	No suitable substitute because of high freezing point	No suitable substitute because of CMR classification	No suitable substitute because of CMR classification and high freezing point

In addition, other parameters need to be verified with regard to their compatibility, too, i.e. solvent compatibility with acetylene and porous mass, solving capacity, volume expansion etc.

Currently, there are no suitable alternatives for DMF in this application. Other solvents bearing similar solubility coefficients, have a much higher vapour pressure, e.g. acetone with a vapour pressure of 30.6 kPa at 25°C. Thus, relevant amounts of acetone would evaporate with the acetylene, making it hence not suitable for applications in which a high purity of the acetylene is required. Also, it is possible that the whole amount of acetone evaporates prior to acetylene being used up. This would leave considerable amounts of acetylene unstable, endangering human health, e.g. by an explosion. Furthermore, DMSO is not a potential substitute for solvent at ambient temperature because of its freezing point (18.5°C). Despite a possibly suitable low vapour pressure, DMSO is very likely to be freezing during transport, e.g. at night or during winter, eliminating it as alternative. Also, e.g. NMP and DMAc have the same hazard (H360D) and are not considered as alternative substance. In general, no alternatives were identified so far with the same characteristics (low vapour pressure and high solvent capacity). To discover and develop a new solvent for acetylene is both time consuming and expensive (assuming it is theoretically possible given the likely restriction on NMP & DMAc). For example the development of DMF cylinders (BAM type testing) took 10 years and its adoption by the end users is still occurring 10 years after introduction i.e. 20 years total. Evidence for this slow adoption is that the specialist market for DMF based acetylene users is growing in the EU whilst the general industrial acetylene market is decreasing. (DMF Consortium, 2014).

C.1.1.3 Solvent in the Plastics Industry

C.1.1.3.1 Polymers

Besides DMF, NMP, DMAc and DMSO are all good solvents for many polymers and are often used in preparing polymer solutions; sometimes acetone, MEK or triethylphosphate (TEP) can be found as solvents, too. Whether and to which extent these alternatives are suitable in the various applications will be discussed in detail below.
Generally, the kinetics of a polymerization reaction, effectiveness, chain length and hence the later performance of the final polymer are strongly dependent on the solvent used. Patra et al. showed on Poly(methyl methacrylate) (PMMA) that the glass transition temperature is significantly influenced by the solvent. Both the thermal and mechanical properties of the PMMA samples appear to be strongly influenced by the choice of the solvent used for the preparation, due to its polarity and to its capability of forming H bonds with the polymer. In particular, for the PMMA samples prepared from chloroform and toluene solutions the glass transition temperature was 20–25°C below that of bulk PMMA, whereas for the PMMA samples prepared from DMF solution it was ca. 10°C above. The PMMA samples prepared from the DMF solution also showed higher reduced modulus and lower creep effect with respect to the samples prepared from chloroform and toluene solutions (Patra, 2011).
In a study by Sánchez-Soto et al., the polymerization of acrylonitrile to polyacrylonitrile (PAN) has been studied using several solvents: N,N-dimethylformamide (DMF), hexane, toluene, water, and in bulk form (no solvent). The addition of DMF is the only case where both monomer and polymer are soluble in the solvent. The polymer samples obtained when using water or toluene as solvents have the greater content of amorphous components compared to the others. The amide molecules are difficult to completely eliminate in the product obtained after the polymerization reaction and even after prolonged heating at 110°C and remain occluded. DMF can be considered to exert a plasticized effect on PAN and is even capable of forming complexes by dipolar bonding. As a result of this interaction, the differential scanning calorimetry (DSC) diagram is quite different from the other samples studied in the present work, showing a single sharp exothermic peak. This is associated with nitrile group polymerization of PAN, i.e. cyclization, instead of melting (Sánchez-Soto, 2001). Hence, it can be concluded that DMF exhibits unique properties in polymer chemistry, making it hardly replaceable. Every alternative method needs to be carefully developed and evaluated, strongly dependent on the unique property and process.

Generally, solvents used in polymer production can be re-used to a very high extent. DMF is used as solvent to produce perfluoroalkylvinylethers (PAVE), which are constituents of different fluoropolymers, Here, one is enabled to recuperate and re-use about 65 % of the solvent used (DMF Consortium, 2014).

C.1.1.3.2 Polyurethane Production

In polyurethane production, remarkable differences in the performance of the final polymer / coating can result from the application of different solvents, which will be outlined further using several examples below.
Polyurethane elastomers (PU) are high-performance materials, and PU-coated fabrics now find applications in inflatable structures, conveyor belts, protective coatings, biomaterials etc. (Oprea, 2005). Oprea studied the influence of solvent interactions on the properties of polyurethane films. In the case of thermoplastic elastomers, their characteristic behavior is caused by their unique morphology. Therein, virtual crosslinking replaces covalent crosslinks, which are the result of hydrogen bond interactions between C=O and N–H from urea or urethane groups. They are segmented polyurethanes consisting a dispersed hard phase (urethane or urea groups) in a soft phase, e.g. a polyol or polyester. Very different network structures can be achieved from the same polymer chains by changing the composition of the precursor solution via a change in the amount of solvent and/or the nature of the solvent. In the study of Oprea, Polyurethane elastomers based on 4,4-methylene-bis-phenyl isocyanate (MDI), polyester diol obtained from ethylene glycol and adipic acid and ethylene glycol as chain extender were synthesized by the conventional two-stage polymerization method. Various solvents

were used as reaction media: N-methyl-2-pyrrolidone (NMP), dimethylformamide (DMF) and mixtures of NMP with DMF, toluene, and ethyl acetate (at a rate 80/20 weight). These polyurethanes exhibited different behaviors due to different interactions between solvents and macromolecular chains or solvents and water. Polyurethanes that were obtained in NMP show better mechanical properties, indicating that NMP is a better solvent for polyurethanes than DMF, toluene or ethyl acetate. For example, lower values of the tensile strength and elongation for polyurethane based on DMF in comparison with polyurethane based on NMP can be observed, which can fact can be explained by the formation of hydrogen bonds (NH...O=C<) with a much higher frequency in the case of NMP.
Consequently, by changing the solvent, polyurethane films with different mechanical and thermal properties can be obtained (Oprea, 2005). In conclusion it means that, dependent on the unique process and the required properties of the polyurethane film, solvents including DMF cannot be replaced at all.

In the industry, there are widespread applications involved in the production of polyurethanes, starting from the production of the polymer, incl. spreading or more generally shaping of the polymer, re-solve of the precipitate in order to produce e.g. PU coatings with pre-defined properties etc. DMF is generally used as solvent in various processes. Examples from industry include e.g. spreading processes of PU und TPU resins for adhesives, coatings, or multilayer film, for which no alternatives are available for the production of these items with identical properties. It is often used to solve pre-manufactured PU or TPU chips or granulates, to dilute PU formulations, for the preparation of coagulation and transfer coating recipes. Thereby, e.g. PUR textile-coatings for use in medical and protecting materials or PUR films/ foils for technical applications (membrane films) are produced. Taking PU in solution generally allows e.g. its coagulation in water. Alternative products for the production of coagulated material and at least 80% of coated material, do not exist yet. Based on the current knowledge it is unlikely to impossible to manufacture products with similar properties, using possible alternatives, such as methylethylketon or water-based solutions. After finishing the production of the respective product, the DMF used in processing is recovered trough water scrubbers, distilled and reused infinite times. Consequently, no DMF stock-up is necessary, clearly demonstrating the minor amount of residual solvents in the final product, as well as negligible emission into the environment or exposure of workers. (DMF Consortium, 2014).

C.1.1.3.3 Artificial leather

DMF is also used as solvent in production of polyurethane elastomers in solution especially destined in the leather industry, more generally in the textile industry (ECHA, 2012). In Italy, e.g. about 1000 employees are working in the artificial leather industry. Generally DMF is mainly used as a solvent in a closed process, no significant exposure for humans is given.

Polyurethane mixes are either purchased as solutions in DMF or prepared on-site, where they are blended with film forming ingredients and other solvents to produce coating lacquers. DMF is used here as a solvent to dissolve polyurethane granulates and to dilute polyurethane solutions; commonly available are e.g. solutions of ± 38% PU dry matter in DMF. These coating lacquers are then coated as thin layers usually onto textiles. Other applications for coating of textiles are e.g. PVDF- and Acrylic clear coats for PVC-coated polyester materials. The fluoropolymer PVDF is essential in premium membranes for textile architecture. As of now no PVDF clear coats PVDF without DMF or NMP are established in the market. After application, the solvents (including DMF) are dried off in hot air ovens to leave a dry polyurethane layer. The most important applications are technical garments, mattress protectors and imitation leather for upholstery. DMF is the only solvent capable of dissolving high molecular weight aromatic TPU (DMF Consortium, 2014).

DMF is used as solvent for TPU production, mainly in the coagulation process (production of synthetic leather for bags, shoes, furniture, or automotive). For this specific use (coagulation) other solvents are not suitable as substitutes. The DMF is shot down and recovered by distillation in the factory of synthetic leather production. It does not exist a polyurethane water soluble solvent for coagulation process, recoverable with water and distillable with actual distillation plant that have a low toxicity and high boiling point (DMF Consortium, 2014). Alternative solvents have not the properties for the

coagulation process and are dangerous like DMF, more difficult to handle, bearing higher flammability risk (less flammability temperature), and there is a minor possibility to be treated in recovering/distillation plants (DMF is recovered up to 99,99% and re-used in the same process) (ECHA, 2012). The required technical characteristics mechanical resistance, breathability, and conformability are not sufficiently achieved by alternative solvents (ECHA, 2012). E.g. chemical resistant to cleaning and disinfection, thermoplastic behavior, etc. can only be realised by (aromatic) polyurethane coating for which DMF is an essential solvent (see chapter C.1.1.4.3, Polyurethane and other polymer films in wound dressings) (ECHA, 2014a).

The potential alternatives to DMF as solvents for polyurethanes which could eventually be taken into consideration due to their nature of a bipolar aprotic solvent were identified to be the ones listed below. However, it must be noted that the suitability of a certain solvent strongly depends on the required properties of the finished material. So e.g. “the suitability in polyurethane production” cannot be generalized, but must be considered on case-by-case basis.

- Toluene (CAS 108-88-3): It cannot be considered as candidate due to its poor solvent power, unable to solve the Polyurethane elastomers. Also currently Toluene is classified as toxic for reproduction category 2 According to Regulation EC No. 1272/2008 (ECHA, 2012).

- N-Methylpyrrolidone, NMP (CAS 872-50-4) is a suitable solvent by technical point of view and already used in polyurethane synthesis but it classified toxic for reproduction category 1B acc. to Regulation EC No. 1272/2008 like DMF and already candidate to SVHC list. Hence, it cannot be considered as alternative (ECHA, 2012) due to its high toxicity, although being suitable for some uses. In addition, its costs are much higher than the ones of DMF (DMF Consortium, 2014).

- N-Ethylpyrrolidone, NEP (CAS 2687-91-4) is likely to be put on the SVHC list soon, also, the price of NEP is multiple of price of DMF (ECHA, 2012). Also, taking into account its high boiling point of 212°C, the removal by drying of the final PU product is made rather difficult. Consequently, it cannot be considered as alternative.

- N,N-dimethylacetamide, DMAc (CAS 127-19-5): It is in candidate list and recommended for inclusion in Annex XIV due to its classification toxic for reproduction category 1B acc. to Regulation EC No. 1272/2008 (ECHA, 2012) furthermore eliminating it as alternaitive. Also, the performace of this solvent is way too different from DMF, which do no allow the manufacture of similar products (DMF Consortium, 2014)(see chapter C.1.1.1.3 Fibre Production).

- Tetrahydrofuran, THF (CAS109-99-9): There is not any possibility to use it as solvent due to its limitative or non-existing dissolving power for Polyurethane elastomers (ECHA, 2012). Also, it is a solvent that may generate peroxides, complicating product formation substantially, and its use is not recommended because of its explosive nature and it is multiple times higher in price vs. DMF. According to ECHA’s dissemination website, it is also classified as STOT SE 3 (respiratory irritation, affected organs: central nervous system) and as carcinogen cat. 2. So it is no alternative at all (ECHA, 2012).

- Dimethylsulfoxide, DMSO (CAS 67-68-5): Although not being classified as toxicant to reproduction and bearing a solvating capability comparable to DMF, it is affected by important limits as the high melting point at 18°C, this feature excludes the use in application processes for Polyurethane elastomers because no any of the existing plants are able to handle solid products at room temperature. Furthermore, due to its high boiling point (189°C) it requires higher operating temperatures and hence more energy. Most available plants are incapable of handling technological processes at this elevated temperatures, and similarly to NEP, the removal by drying of the final PU product is rather difficult. This solvent is also corrosive and this is another excluding condition for the existing plants in application, as this

would require new ovens to be build from stainless steel. Summarizing, the physical and chemical properties of DMSO are different from DMF, so the possible substitution would require a radical modification in all the productive chain, from transportation through packaging, to final application plants. Moreover the current DMSO availability is poor, estimated below 5.000 tons/y and unable to satisfy the theoretical demand of the market. In addition, currently the price of DMSO is three times higher than DMF (and expected to be rising upon higher demands), so it is not sustainable economically (ECHA, 2012). It has been extensively tested, but showed poor technical performance. It was considered unsuitable i.a. because of the colour stability of clearcoats and hygroscopic behavior (DMF Consortium, 2014).

- Other solvents: Those include i.a. butanone (methylethylketone, MEK), Methylisobutylketon (MIBK), hexane, isopropanol, heptane, ethylacetate, etc. These however are not polar enough to dissolve for instance the high molecular weight TPU's. Due to this limited dissolving power, DMF cannot be replaced with another solvent with the same dissolving power and that does not appear on the SVHC list for dissolving the polyurethanes. Taking into account their respective prices, there is no substitute at all (ECHA, 2012).

- Water-Based PU coatings: The performance of current solvent based coatings can not be achieved with waterbased systems for required applications, i.e. coating and lamination of textile in various industries such as the medical, industrial and food industry. The difference in performance is tremendously. In terms of processing, it is known that the waterbased systems run at a much slower speed as compared to solventbased systems. In addition the ovens need to be replaced by stainless steel ones due to corrosion and the waterbased systems are much more expensive (ECHA, 2012). Moreover, chemical resistance to disinfection or sterilization is not be reached, which is a necessity for high performance technical textiles such as protective clothing. Artificial leather in solvent-less polyurethane has too low abrasion values and mattress covers in water based polyurethane have no resistance to washing at 95°C which make these products useless for certain applications.

- Solvent-free systems: Those represent technology shifts. Only recent studies already revealed that there can not a straight substitution of solvent based systems by solventfree systems; the ultimate performance of the coatings are completely different often inferior in performance. Hence, there are no available substitute technologies that can take over the solvent based coating technology to build the products currently available on the market (ECHA, 2012).

Generally, DMF is recovered within the plant, usually within an internal destillation's plant.

In consequence, DMF may not be replaced conventionally. It should generally be taken into account that, although DMF may be restricted in the EU, it still can be used outside the EU. If DMF is banned then the business will likely leave the EU. This means that a Chinese or Indian manufacturer will take the business and supply to coating operations outside the EU (DMF Consortium, 2014), which will not raise the protection level of workers in general, as intended, but only shift the problems to other countries, in which health and safety measures may even not have such a high priority as in the EU. Consequently, the ban will only have negative impacts on the EEA as well as on health and safety of workers.

C.1.1.3.4 Polyurethane curing and removal

Another issue on Polyurethane is the removal of the cured coating, e.g. for recycling issues. Polyurethane resins find wide use in a variety of industrial applications. They are a class of polymeric, synthetic resins, that can be cured in accordance with well known and conventional curing techniques to produce a variety of products such as rigid, semi-rigid or flexible foams; hard, glossy coatings relatively resistant to solvents; rubbery and fibrous materials; as well as thin, paint-like compositions. Perhaps their most important use in modern technology resides in their application as cured foams in rug

backing, upholstery material for furniture, commercial and residential insulation and as insulating materials for aircraft components. The cured polyurethanes also are of importance as conformal coatings and foam encapsulants for electronic circuit boards and other electronic components (Elwell, 1983). Polyurethane resins however are solvent-resistant, bearing several problems and the need to develop a solvent mixture that would be effective in dissolving and removing cured polyurethane resins whether in the form of a thick coating, paint-like coating, foam encapsulant or foamed structure, in order to avoid economic losses, hazardous health conditions from corrosive solvent vapours and health hazards from the pyrolsis of conformal coatings. As a consequence, Elwell, Jr. found that a solvent mixture containing dichloromethane, dimethyl formamide and methanol resolving strictly through solvent activity without the need for an additional abrading or grinding action, which often results in excessive damage to polyurethane coated, electronic components.
The solvent mixture's effectiveness appears to reside in its ability to achieve slight solvation with maximum swelling (Elwell, 1983). These properties however are not expected to occur without DMF contained. Currently, no alternatives for the described solution with similar effectiveness are known. Alternatives, however being less effective, are usually methanol base / alkaline activator solvents. Methanol, however, is still classified as STOT Single Exp. 1 according to Regulation (EC) No 1272/2008 due to its effects on the central nervous system, and alkaline activators are most commonly based on sodium hydroxide (Wollenbrinck, 1993), which is classified as corrosive, and is hence not only endangering human health but also may damage the underlying circuits. Further alternatives to DMF could be THF, Toluene, HFIP, DMSO, or Chloroform, which are either similarly classified as DMF and / or lacking a similar performance.
In conclusion, not suitable alternative with similar performance to a DMF mixture is available.

C.1.1.3.5 Membranes Production

Membranes are required for many applications including reverse osmosis, ultrafiltation, or nanofiltration. They are commonly manufactured by precipitation of a polymer from a polar solvent like DMF. Similarly to other Polymer products, the production of membranes with specific properties is highly dependent on the applied solvent.
Examples could be the production of an isoporous integral-asymmetric polymeric membrane, i.e., an ultrafiltration membrane or nano-filtration membrane or an isopore integral asymmetric polymer membrane, as described by Peinemann, 2014. For membranes, a wide dispersion in the distribution of pore size has two disadvantages: Firstly, such a membrane does not allow precise separation of a mixture of substances to and on the other hand tends such a membrane to the so-called fouling. membranes with a small dispersion in the distribution of their pore size, i.e. isoporous membranes, are required. One specific example is given for a process with precisely defined Polymer / solvent mixture, i.e. 20% polystyrene-b-poly-4-vinyl pyridine (PS-b-P4VP), 20% tetrahydrofuran (THF), and 60% dimethylformamide (DMF), which would result after spreading, immersion in a water bath and drying in a perfectly isoporous membrane as shown in Figure C3:

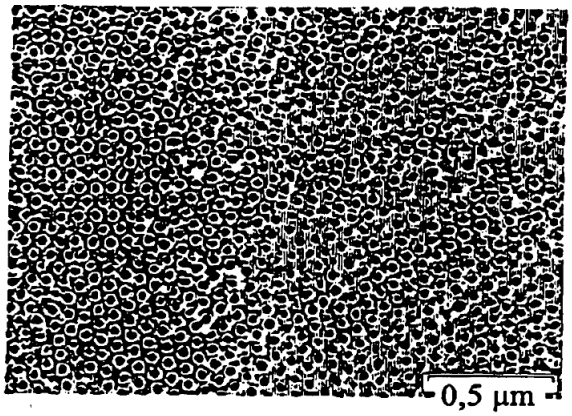


Fig. C3. Isoporous membrane produced from a tailor-made solvent composition containing mainly DMF (taken from Peinemann, 2014)

Isoporous membranes may be also manufactured e.g. by electrolytic oxidation of aluminum. A major disadvantage of these membranes is proving that they are very fragile and very expensive (Peinemann, 2014). Consequently, also here DMF cannot be replaced without loss of high performance of the membranes.

Related results were obtained by Osińska-Broniarz et al., 2014. They produced polyvinylidene fluoride/hexafluoropropylene copolymer (PVdF/HFP) membranes to be used with gel electrolytes for lithium-ion batteries. They applied four different methods for the production of the PVdF/HFP membranes: a two-step method involving modification of two-step Bellcore process in which the PVdF/HFP copolymer was dissolved in acetone butyl phthalate was added as a plasticiser to the system (A), an inversephase process using a mixture of DMF and glycerol (B) or NMP and acetone (C), and a method of gel electrolyte production dissolving of PVdF/HFP in acetone and placing it afterwards in a vessel with steam (D). All mixtures were poured onto a surface and dried. Figure C4 shows images of the respective surfaces applying scanning electron microscopy (SEM):

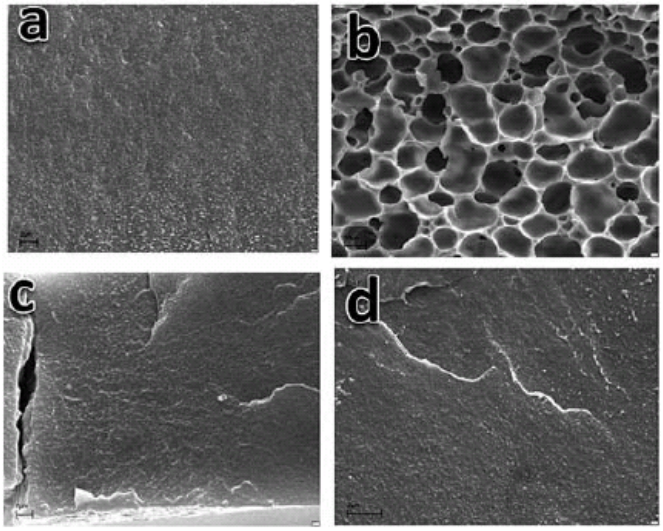


Figure C4: SEM images of PVdF/HFP membranes using various production processes: a) Bellcore process; b) using mixture of solvents: DMF and glycerol; c) using mixture of solvents: NMP and acetone; d) using steam (taken from Osińska-Broniarz, 2014)

As it can be seen in figure C4, the membrane produced using modified Bellcore method (a) has a porous structure, in which the diameter of individual micropores is below 2μm. The membrane produced using DMF and glycerol (b) has high porosity and the diameter of individual pores is in range of approximately 10–15 μm. Polymer membranes produced using NMP or steam (c and d, resp.) show a very homogeneous structure. No micropores were observed in these structures (Osińska-Broniarz, 2014).

Tabe-Mohammadi et al. prepared cellulose acetate membranes with casting solutions, with acetone, DMF, and NMP as solvents and applied them in a series of methanol/methyl tertiary butyl ether separation experiments. The flux and selectivity of the membrane samples were affected by the type of solvent used to prepare the casting solution. The sample with DMF consistently gave the highest selectivity and lowest flux, followed by the samples with NMP and acetone. The differences in the performances were attributed to the effects of the volatility and evaporation rates of the solvents. Also, alterations of morphology were observed by SEM, dependent on the respective solvent (Tabe-Mohammadi, 2001):

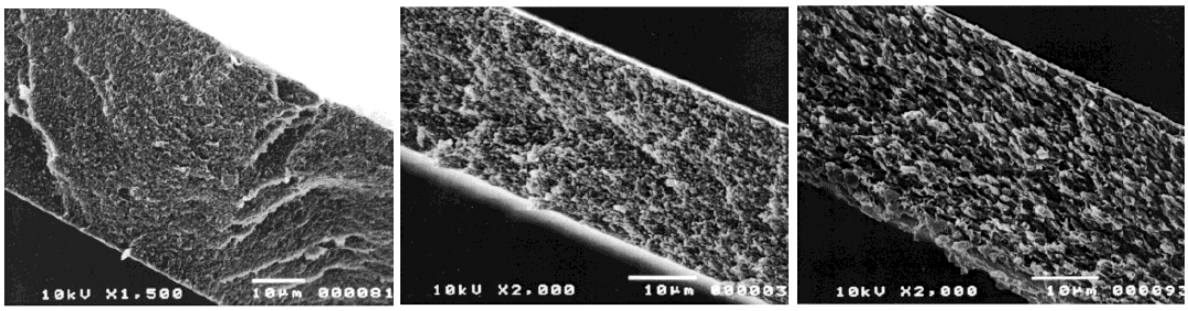


Figure C5: SEM images of cellulose acetate membranes prepared with different solvents: Acetone, DMF, and NMP (taken from Tabe-Mohammadi, 2001)

These examples underline perfectly the differences obtainable from the same polymer applying different solvents and production processes. In consequence, dependent on the required properties of a membrane, DMF may not be replaceable.

C.1.1.3.6 Fiber Production

Besides the production of thin polymer layers, such as polyurethane coatings or other polymer membranes, DMF is also used as a solvent in the production of polymeric fibers. It is used as a spinning solvent for e.g. polyacrylonitril (PAN); PAN fibers are the most common ones. The PAN precursor e.g., to describe the general process, is dissolved and the resulting 'dope' solution is forced through a spinnerette and into a water bath. At this point the solvent dissolves into the bath and the polymer precipitates as a monofilament fiber. The fibers are in general not sold to end users, they are delivered to dye houses and spinning mills. Also, the dissolved solvent is afterwards recycled internally. Especially DMF is generally easily manufactured and recovered in this production process.

An alternative production process for fibers, if the melt spinning process is not applicable, is the so-called dry-spinning process. It is used in cases where the polymer may degrade thermally if it is attempted to melt it, or in cases where certain surface characteristics of the filaments are desired, e.g. melt spinning produces filaments with smooth surfaces and dry spinning produces filaments with rough surfaces. The rougher surface may be desirable for improved dyeing steps or for special yarn characteristics. The polymer dissolved in a volatile solvent (dope) is then extruded through a spinnerette as filaments into a zone of heated gas or vapour. It is hence important to heat the air above the boiling point of the dope solvent. The solvent evaporates into the gas stream and leaves solidified filaments which can be collected on a take-up wheel. A very common product derived in the dry-spinning process is the acrylic fiber which is dry spun commercially in large volumes.

For the production of the respective fibers, the parameters solubility, milling properties and curing of the manufactured fibers are relevant for the aimed product quality. Generally, there are other alternative solvents available, but certainly those are accompanied with perceptible constraints:

The low ignition temperature of DMAc of 345°C compared to DMF (410°C) leads to a constraint in the achieveable spinning efficacy because the air temperature during spinning at the entrance of the polymer solution into the hot air is limited to max. 300°C, resulting in a reduction of the spinning capacity to 70%. DMAc has a higher solvating power than DMF, which leads to an enhancement of the viscosity of the solution compared to DMF at identical polymer concentrations. With increasing titer this results in a higher residual solvent amount in the final product. The resulting costs from the modification of the dry spinning process, i.e. exchanging DMF with DMAc, would lead to diseconomies of the process. DMAc may be also applied in the wet spinning process; however, this would lead, as described above, to different fiber characteristics (Petereit, 2014).

In the past, within the context of PAN fiber production, the influence of either DMF or DMSO as solvent was subject to various studies:

During optimization of the different production steps in the production of PAN fibers, certain requirements must be fulfilled already during the polymerization process, especially with regard to the effective speed and achieveable degree of polymerization. These two factors were influenced by the polymerization medium, which must be simultaneously the solvent for polyacrylonitril. At first sight, DMSO seems favourable compared to DMF regarding both the effective speed and diminished chain formation constant. Via an adequate choice of the polymerization conditions these difficulties however can be compensated and the advantages of DMF can be utilized, such as the lower viscosity of the spinning solution with comparable polymer concentration, the diminished tendency for coagulation and lower evaporation heat (Philipp, 1971; Petereit, 2014).

Dependent on the conditions of the process and material, the properties of PAN fibers may vary tremendously. This is due to the fact that the production of PAN fibers allows a larger amount of variations in material and process parameters of both technical and chemical nature compared to other synthetic fibers. Hartig describes in his report that also precipitation or solvation polymerization allow the modification of fiber properties. Also, DMF solutions exhibit a way lower viscosity than both DMSO or DMAc solutions (Hartig, 1973; Petereit, 2014).

Furthermore, despite the fact that DMSO on its own does not bear similar hazardous properties as DMF, one may need to take into consideration that in combination with other substances it can pose a high risk. Due to its oxidizing properties, corrosions and exothermic reactions leading to explosions may occur, e.g. in combination with caustic potash which led to the expolsion on 8th July 1999 at Bayer AG in Wuppertal-Elberfeld. Furthermore, DMSO exhibits a percutaneous carrier effect enableing other substances to penetrate the skin more easily in the presence of DMSO (Petereit, 2014).

DMF is not only used in the production of fibers themselves, but also as a solvent in fiber coating (see chapter C.1.1.3.7 Coatings production). An example would be its use as a solvent based resin (PU/DMF) for fiber impregnation, e.g. in the production of strings for Tennis and squash rackets. An already evaluated alternative her would be DMSO. Besides its influence on the product performance, i.e. a negative impact on its lifetime, other negative impacts on the product quality such as undesired odor have been observed (DMF Consortium, 2014).

C.1.1.3.7 Coatings Production

DMF is made from the reaction of DMA and carbon monoxide or methyl formate. Its uses include urethane coatings, spinning solvent (primarily for acrylics), reaction solvent, extraction solvent (such as butadiene extraction), and processing solvent (including solvent for dicyandiamide for epoxy-laminated printed circuit boards). Coatings include textiles, membranes or coatings in the automotive industry and wire coating for different applications.

For Polyurethane (PU) and Thermoplastic Polyurethane (TPU) DMF is used as a solvent for coating of several types of textiles. Depending on the type of alcohol-based solvent used, the effect on a TPU may differ. Aliphatic alcohols such as ethanol and isopropanol can trigger slight swelling. More obvious levels of distortion can occur with exposure to aliphatic esters and ketones including acetone, methyl ethyl ketone (MEK) and cyclohexanone. Strong polar organic solvents like dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO) can dissolve TPU altogether. (Huntsman, 2014).

DMF is also used as a solvent for many vinyl-based polymers in the manufacture of films, fibres and coatings, and as a booster or cosolvent for both high molecular weight polyinyl chlorides and vinyl chloride-vinyl acetate copolymers in the manufacture of protective coatings, fims, priting inks and adhesive formulations (WHO, 1989).

In general, the polymers are dissolved in DMF and applied to the surface of the textiles or other surfaces. PU resins in DMF are formulated in batch operations and solvent is removed during processing to make consumer goods. Cured (solidified) resins form strong flexible films or “skins” that are scratch-resistant and resistant to the attack of water. These polyurethane films or “skins” range from

very soft and pliable to stiff to suit a wide variety of applications. Polymer coated articles are mostly consumer goods and include i.a.

- Footwear (e.g., uppers for shoes and safety shoes)
- Upholstery – furniture (e.g., sofa), automotive (e.g., dashboard, gearshift, etc.)
- Apparel and accessories (e.g., handbags, belts, etc.)
- Bags, linings, general purpose
- Garments (e.g., labels, jackets, etc.)

Some special solvent-Based Adhesives (TPU) provide a wide range of resins that can be dissolved in solvents such as MEK (Methyl Ethyl Ketone), DMF (Dimethyl Formamide), Ethyl Acetate, Acetone, and Toluene depending on targeted applications and/or economic requirements (Lubrizol, 2014). Thus, DMF is not the only applicable solvent but use depends on the field of application for coatings.

DMF is one of a group of chemicals known as the volatile organic compounds (VOCs) which are considered to be involved in the formation of ground level ozone which can cause damage to crops and materials. The American Coatings Association Inc (2010) report the availability of VOC-free polyurethane dispersions and oil-modified polyurethanes, available from various producers of composites and polymers, which can be formulated for wood, textile, leather, concrete, bitumen and other applications. However, the substitution of DMF by other solvents, e.g. acetone or dipropylene glycol dimethyl ether (DPGDME), is only possible for special applications and cannot substitute DMF at all applications. In addition, DMF is present at manufacture of industrial coating and will be stripped off usually in a closed system (ACA, 2010).

The coating of wires is another important use of DMF as a solvent. Wires are coated by different polymers like polyvinyl acetal, PU, polyurethane with a polyamide top coat, THEIC modified polyester, aromatic polyimide (ML) or fluorinated ethylene propylene (Sandvik, 2013).

Polyamideimides (PAI) and polyimides (PI) are soluble in dipolar aprotic solvents such as N-methyl pyrrolidone (NMP), dimethyl acetamide (DMAC), dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO). Only a few coatings are soluble in water. The solubility of the more thermal and solvent resistant polymers such as PAI, PI and PVDF, make the amount of possible alternatives limited to the ones mentioned above: DMF, DMAC and DMSO for PAI and PI. Solvents for PVDF are dimethyl formamide (DMF), dimethyl acetamide (DMAC), tetramethyl urea, dimethyl sulfoxide (DMSO), triethyl phosphate, N-methyl-2-pyrrolidone (NMP) and acetone.

Based on the literature available, it cannot be clearly decided whether or not DMF can be completely substituted. Information from industry is not available yet. The use of DMF for the different types of coatings is strongly depending on the polymer used for coating, the material to be coated and the poperties to be achieved. Some applications of DMF as coating solvent may be substituted by water or organic substances. However, specific coatings will depend on the solvent DMF.

C.1.1.4 Solvent for medical devices manufacture

C.1.1.4.1 Medical Devices – General

The use of solvents in medical device production can be summarized in manufacture, coating and cleaning. The main focus on every type of medical device is the biocompatibility. Thus, solvent residues are strictly regulated. In evaluating alternatives, users of these materials must balance the need for cost-effective performance with that of a sustainable, long-term solution – a solution that will still be viable for many years to come.

In the context of medical devices (MD), solvents are used for a wide variety of coatings and lubricants – including silicone, fluorocarbons, PTFE and heparin. Solvents need to bear low surface tension, low vapour diffusion rates and high liquid densities for use in vapour degreasing equipment. Thus, DMF is

not the major solvent in MD manufacture and is limited to a few applications. However, these applications need the specific physico-chemical properties of DMF. Medical Devices are regulated by Directive 93/42/EWG; all products that are relevant for this SEA are CE marked according to this regulation. There are strict regulations for the documentation of such products. Changes in raw material require a total revision of documentation and a lot of testing and validation has to be redone. Compiling all the information and certification by a notified body is a costly and time consuming process.

The major applications of DMF are adhesives and coatings, e.g. polyurethane coating. Even DMF is not the only solvent used in MD manufacture, in specific applications only the unique properties of DMF will result in the desired product.

C.1.1.4.2 Polyurethane in medical devices

The advantage of polyurethanes (PUs) is that they can be used in applications where other materials do not work. PUs are tough, biocompatible, and hemocompatible. Several types of polyurethane are appropriate for medical applications, including the following:

- Liquid polyurethanes for hollow-fibre devices.
- Polyurethanes for dip-molding.
- Polyurethane coatings.
- Biostable polyurethanes.
- Thermoplastic polyurethanes.

One of the important uses of PU is the manufacture of antifouling PU coating for MD (Francolini, 2014) or hydrophilic polyurethane coatings (Köcher, 2011). The use of solvents in the manufacture of PU is a critical step since additives and stabilizers of the solid PU can be removed (Vermette, 2001). Due to the universal properties of DMF in high purity, this solvent is used for manufacture of these PUs.

PUs are used for coating of several types of MD, e.g. stents, specific implants or wound dressings.

C.1.1.4.3 Polyurethane and other polymer films in wound dressings

Mainly DMF, but also other dipolar aprotic solvents, most of them similarly classified, are used in the manufacture of polyurethane coated wound dressings. The use of DMF is necessary to dissolve the special polymers required to provide the technical product characteristics sought by customers. These have been shown to have significant clinical benefits resulting in improved patient care (ECHA, 2014a), as will be outlined below.

Generally, for the manufacture of breathable polyurethane films that are used as components of advanced wound dressings for the medical industry, the required polymers are applied in solution. The polyurethane mixes are dissolved in a blend of solvents, one of which is DMF. The films are manufactured by casting the polyurethane mix onto paper or plastic film and drying off the solvents in hot air ovens (ECHA, 2014a).

The following properties are required for polyurethane coating in medical wound dressings:

- Moisture resistance: The polymer must not be soluble in water. First, wound secrets and other body fluids are coming into contact with the coating may not resolve it, in order to avoid direct contact with the bandage or gauze, which could result in a secondary infection due to bacteria, dirt or other chemical substances entering the unprotected wound. Second, the wound dressing needs to persist several days in order to allow the patient to perform the usual body hygiene, e.g. shower, while staying at home without the need to visit the hospital regularly for a change of the wound dressing. One of the key advantages of breathable polyurethanes coated by EAC is that the dressings made utilizing these materials can stay in place, without the need for nursing intervention, for four days or more. Although a traditional dressing is less expensive

than one based on DMF-produced polyurethane, nursing intervention (dressing changes) are required every day. Reducing nursing intervention does not only improve life quality but also avoids secondary infections due to the often change of the dressing and hence the opportunity for infection of the wound during dressing changes is minimised (ECHA, 2014a). In addition, if possible at all, essentially slower production rates are achieved by water-based solutions. As a result, water or aqueous solvent mixtures cannot be applied in the manufacture of wound dressing coatings (Shadbolt, 2014).

- Solvent and radiation resistance: Generally, wound dressings are sterilized, which is usually achieved by γ-irradiation. Hence, the PU films needs to resist that treatment. Furthermore, during wound treatment, surgery or exchange of the dressing, the treating physician or hospital personnel are using various disinfectants, mostly on basis of propanol, isopropanol, or ethanol. Consequently, the PU film also must resist those solvents which hence cannot be applied in manufacture of PU films (Shadbolt, 2014). This is also applicable for solvents with similar properties, e.g. butanol or methanol.

- Defined permeability for moisture: The coating must not be impermeable to moisture. The wound is secreting fluids as well as the normal skin is sweating, which would result in a moist environment of the wound which could first lead to a hindered wound healing and second to an infection of the wound. Hence, the coating must be permeable. However, it should not completely leave the wound dry, as certain moisture is required for wound healing. Consequently, a defined permeability is needed, which could be only achieved by using the proper solvent. The water permeability results from the hydrophilic side chains of the polymeric backbone, less from the possible pores in the material, which can only be achieved in general by dipolar aprotic solvents, solving the hydrophilic and hydrophobe moieties of the polymer and its precursors (Shadbolt, 2014). There are clinically proven advantages versus non bacterial barrier and non breathable systems. Many papers have been written showing the advantages of advanced woundcare products over “traditional” dressings (ECHA, 2014a), clearly emphasizing the importance of defined moisture permeability, which can only be achieved by a PU production employing DMF.

- Microbial barrier: As a wound barrier, the polyurethane film is not allowed to contain pores enabling bacteria to enter the wound. Also, since the PU film will be coated after production, pores are not allowed in order to avoid any wholes in the coating. By applying DMF as solvent, pores that are not greater than 15 µm can be achieved. Currently, this property is not known to be achievable by other solvents (Shadbolt, 2014). Most of the material sold is utilised in dressings that are used in a hospital environment, mostly for the treatment of chronic conditions in the elderly, where infection control is of paramount importance. The materials provide a bacterial barrier and therefore help to control infection. Other materials could provide a bacterial barrier but the DMF based polyurethanes are breathable (ECHA, 2014a). This importance was already outlined above.

- Negligible content of possible skin-permeable process solvents: Medical products manufactured using DMF are cast polyurethane films which are dried to a controlled level of retained solvent. Product specifications and testing methods are designed to ensure levels of DMF in the finished films are maintained below 0.1%. In practice retained solvent levels in films leaving the production unit are typically around 0.03%. All films are subject to further processing by downstream users and DMF levels in products reaching the general public are much lower still. This has been demonstrated by solvent retention tests on fully processed and sterilised customer samples. According to Exopack Advanced Coatings, there is no risk to intermediate processors, or end users, of the films produced by EAC as the levels of free DMF in the finished products are negligible (ECHA, 2014a). This is only achievable since DMF has a rather low boiling point of 152-153°C at 1013 hPa. As alternatives for the production of these PU films NMP or DMSO were considered (Shadbolt, 2014). NMP, however, bears the same hazardous properties as DMF. Furthermore, the boiling points of NMP and DMSO are ± 204°C

resp. 189°C at 1013 hPa and consequently much higher than the one of DMF. As a consequence, the solvents from the production process could not be removed by simple drying, which would lead to a rather high amount of remaining solvents in the wound dressing. Due to their low molecular weight and dipolar aprotic nature they are both able to cross as the stratum corneum as well as the deeper-lying epidermis or unprotected wound tissue, which would result in an absorption of the remaining solvent. This process needs to be avoided, and since only DMF due to its lower boiling point can be removed from this customized PU film, there is no suitable alternative available.

- Wet strength: The wound dressing needs to exhibit the same properties in both dry and wet state in order to maintain i.a. its intended barrier function. To the current knowledge, only the application of aprotic solvents can ensure this property (Shadbolt, 2014).

Research for alternatives was ongoing for over 10 years, however, no suitable alternative resulting in identical product properties could be identified (Shadbolt, 2014). For some minor relevant products, other solvents, e.g. THF or DMP could be applied, but the unique properties as demanded by both downstream and end users could not be achieved.

The alternative technologies considered over many years, primarily to reduce the DMF exposure risk to employees, have included (see also chapter C.1.1.1.1 Polyurethane Production):

- alternative solvents
- water-based systems
- extruded films

A programme of work was initiated in 2003 to try to eliminate the use of DMF as a solvent. A number of potential alternatives were identified and evaluated but were found to be unsuitable.
The alternatives evaluated to date have not provided a polymer system with functional performance similar to the resin system currently used, as described above. In particular, a film with similar tensile and elongation properties in both the dry and wet state has not been obtained. These are key functional parameters of the polyurethane film and determine the ability to meet end users' requirements in a medical product.
There are a limited number of polar solvents capable of dissolving high molecular weight polyurethane resins. Alternative solvents such as DMAc and NMP are capable of acting as alternative solvents for the current polyurethane type but have similar toxicological hazards as DMF (ECHA, 2014a).

Since the properties described above are imperatively required for PU layer in medical wound dressings, DMF cannot be replaced, which makes a restriction, for which suitable measures are already available, absolutely preferable over an authorization. The consequences of the latter would either be the non-availability of proper wound dressings unacceptably impairing health care, or the transfer of the required plants to non-EU countries. Import into the EU of the finished wound dressings would still be possible as due to the current drying process of the PU layers, no relevant amounts of DMF are remaining in the final article.

C.1.1.4.4 Other Medical Devices and Applications

DMF is also used for in-vitro medical device products, similarly as described above, to dissolve substances, facilitate chemical reactions that would not be feasible or robust in many other organic solvents, and prevent unspecific reactions, e.g. in Latex agglutination test. For manufacturing of IVD medical devices DMF is used as a solvent and a cross-linking agent, e.g. for the coupling of amino acids during the peptide synthesis to manufacture some synthetic chromogenic substrates. For these uses DMF is very difficult to substitute by less hazardous ones, if possible at all. Generally, there are other polar aprotic solvents with similar physical properties that could potentially be used in place of DMF in some API manufacturing syntheses. The most common ‘direct’ alternative is DMAc (N,N-dimethylacetamide). Others include formamide, N-methylformamide and N-methylacetamide.

However, these alternatives also carry essentially the same health hazard as DMF (ECHA, 2012).

Examples of those devices besides the ones described above are Healthcare mattresses. It is vital that these materials remain available as they allow for the prevention and treatment of Pressure Ulcers whilst reducing the risk of Hospital Acquired Infections. Those are covered with polyurethanes exhibiting the correct balance of properties for uses in transfer coated textiles as the patient interface in Class 1 medical devices for pressure area care. For this end use they have to withstand extremely harsh cleaning and decontamination procedures due to the risk of hospital acquired infections. Despite projects to investigate alternatives to DMF since 1999 nothing suitable, with the stretch and recovery performance and resistance to cleaning regimes required, has been found. Research was going, unfortunately without success due to the reasons below, into the direction of:

- DMAc: It exhibits a similar risk as DMF and is also under recommendation for inclusion in authorization.
- Methyl ethyl ketone: Due to its low flash point it is presenting risk to workforce and surroundings; this material is hard to handle and will require capital expenditure and process modification.
- Water: There is no evidence that this product durability will ever meet the product requirements; also, this process will require Capital expense and new apparatus (DMF Consortium, 2014).

In consequence, also here DMF is irreplaceable, as no reasonable alternatives exist.

C.1.1.5 Laboratory Use

DMF is usually used as a solvent for a great many of chemical reactions (see above) in the laboratory as well as for laboratory scale–up trials of industrial synthesis. As a universal solvent, the uses of DMF in the laboratory reflect the use in industrial processes and the scientific research. Besides the use in chemical reactions like SN2-reaction, DMF is also used as a solvent for specific analytical assessment, e.g. Gel Permeation Chromatography (GPC). Thus, DMF use in a laboratory is a very specific application of a solvent for scientific analysis.

The use of DMF as laboratory chemical is considered as a use by professionals (non-industrial use). DMF is known to decompose slowly at room temperature and more rapidly at reflux, releasing dimethylamine and carbon monoxide. This decomposition is catalysed by acidic and basic impurities, and standing DMF for several hours at room temperature with basic drying agents such as calcium hydride or sodium hydroxide leads to noticeable decomposition. DMF is a combustible liquid. Vapours are heavier than air and may travel to source of ignition and flash back. Thus, specific care is taken in every laboratory regarding safe use of DMF.

Due to these hazardous properties of DMF, the laboratory use is restricted by Safety measures, e.g. Standard Operating Procedures (SOP) and work processes descriptions. In addition, employees are trained for the safe use of DMF.

C.1.2 Overall conclusion

Dependent on the specific applications, alternatives may be available. However, for the vast majority of applications, adequate alternatives are lacking. Table C6 provides an overview on the available alternatives for the specific uses. It must be clearly noted that the table below only outlines the availability of alternatives in general, and does not assess the final feasibility of the substitute, e.g. by taking into account the hazardous properties of the alternatives. This will be outlined in detail in chapter C.2 Assessment of Alternatives.

Table C6: Overview on possible substitutes for DMF, dependent on sector of use

Use	Substitutable	Remark

Solvent in SN reactions	Possibly	Aprotic polar solvents required; substitution dependent on specific use
Fine Chemicals	Possibly	Substitution strongly dependent on specific use
Pharmaceuticals	Possibly	Substitution strongly dependent on specific use; Exchange will trigger high costs regarding development and regulatory compliance
Plant Protection Products	Possibly	Substitution strongly dependent on specific use; Exchange will trigger high costs regarding development and regulatory compliance
Butadiene production	Yes	Alternatives known
Extraction solvent	Possibly	Substitution strongly dependent on specific use
Transport of Acetylene Gas	No	No alternative known with similar combination of required properties
Polymers	Possibly	Strongly dependent on the unique required property and process
Polyurethane Production	Possibly	Strongly dependent on the unique required property and process
Artificial leather	Possibly	Substitution strongly dependent on specific use
Polyurethane curing and removal	No	No alternative known
Membranes Production	Possibly	Strongly dependent on the unique required property and process
Fiber Production	Possibly	Strongly dependent on the unique required property and process
Coatings Production	Possibly	Substitution dependent on specific use; available information is limited
Medical Devices – General	Possibly	Strongly dependent on the unique required property, purity and process
Polyurethane in medical devices	Possibly	Strongly dependent on the unique required property, purity and process
Polyurethane and other polymer films in wound dressings	Possibly	Strongly dependent on the unique required property, purity and process
Other Medical Devices and Applications	No	No alternative known with similar combination of required properties
Laboratory Use	Possibly	Strongly dependent on the unique required property and process

C.2 Assessment of Alternatives

The most important applications of DMF are described in detail above. It became obvious that the following properties need to be considered most important when assessing its possible replacement by other substances:

- Nature as polar aprotic solvent: Polar aprotic solvents all have the advantage of being able to dissolve a wide range of substances, but do not have the acidic proton that most highly polar solvents have. They strongly support SN2 type recations since they do not solvate the nucleophile, which could not be achieved by e.g. polar, protic solvents which preferrably lead to SN1 reactions.
- Solvent Capacity: In various applications the solvent needs to exhibit a sufficient solvent

capacity in order to allow a sufficiently economic process or, e.g. in polymer coatins production, it must be capable to solvate the high molecular polymers sufficiently to obtain the desired polymer concentration in solution for the manufacture of a polymer coating with exactly the desired properties. So, the substitute may not be limited with regard to its solvent capacity

- Melting Point: Many reactions and applications are strongly dependent on the process temperature. If a reaction temperature is limited via the melting point of the applied solvent, the reaction may either not be feasible because the required activation energy ΔG of a reaction may not be overcome, or too much energy must be applied to the reaction vessel which may lead to the decomposition of the reactants or strongly exothermic and hence dangerous reaction to human health. Also, one needs to regard the temperature of the environment. If the production site is located in cold areas, in which the ambient temperature is below the melting / freezing point of the substance / solvent and hence changes its aggregation state, this will pose additional problems. The melting point of DMF is -61°C at 101.3 kPa. Hence, the potential substitute must melt / freeze within a similar temperature range.
- Boiling Point: Similar considerations apply here as above for the melting point of a substance. The boiling point of DMF is 152 °C at 101.3 kPa, which must also be the range of the boiling point of a potential substitute.
- Vapour pressure: With a value of 3.77 hPa at 20 °C, the vapour pressure of DMF is relatively low. This does not only limit the inhalative exposure, but also ensures a very high purity in case the solvate is further used after evaporation in its gaseous phase, e.g. acetylene. Alternatives with a higher vapour pressure are hence not suitable here.
- Intrinsic Hazard: Potential substitutes must not bear similar hazardous properties, as hence a restriction or authorization process of DMF would be pointless.

Selection of alternatives for further assessment

Although there was a larger amount of substances mentioned as possible alternatives in the various use, some of them are rather "exotic" and may possibly only cover a not very common single use. Hence, the assessment of alternatives focuses on the more common alternatives, mentioned repeated times, focusing so on predominance as alternative and hence relevance. Since their technically feasibility for the specific use was generally assessed already, their suitability regarding their intrinsic hazard should be assessed in a second step. Table C7 shows the identified possible substitutes and their respective classification, as it can be retrieved from ECHA's Classification and Labelling Database (ECHA, 2014b).

Table C7: Harmonized Classification of DMF and possible alternatives to DMF, retrieved 13 August 2014:

Substance	CAS RN	Abbreviation	C&L Harmonized Classification
N,N-dimethylformamide	68-12-2	DMF	Acute tox: 4*, H312/332 Eye irritation: 2, H319 **Repro 1B, H360D*****
N-methyl pyrolidin-2-one	872-50-4	NMP	Skin irritation: 2, H315 Eye irritation: 2, H319 STOT SE: 3, H335 **Repro 1B, H360D*****
Acetonitrile	75-05-8	ACN	Flammable liquid: 2, H225 Acute tox: 4*, H302/312/332 Eye irritation: 2, H319
Hexamethylphosphoramide		HMPA	**Carc.: 1B, H350** **Mutagene: 1B, H340**
N,N-dimethylacetamide	127-19-5	DMAc	Acute tox: 4*, H312/332 **Repro 1B, H360D*****

Substance	CAS RN	Abbreviation	C&L Harmonized Classification
Hexamethylphosphoric triamide	680-31-9	HMPT	**Muta. 1B, H340** **Carc. 1B, H350**
Benzene	71-43-2		Flam. Liq. 2, H225 Asp. Tox. 1, H304 Skin Irrit. 2, H315 **Eye Irrit. 2, H319** **Muta. 1B, H340** Carc. 1A, H350 STOT RE 1, H372 **
Toluene	108-88-3		Flam. Liq. 2, H225 Asp. Tox. 1, H304 Skin Irrit. 2, H315 STOT SE 3, H336 **Repr. 2, H361d ***** STOT RE 2, H373 **
n-Ethylpyrrolidone	2687-91-4	NEP	**Repro 1B, H360D*****
Methyl Ethyl Ketone (Butanone)	78-93-3	MEK	Flammable liquid: 2, H225 Eye irritation: 2, H319 STOT SE: 3, H336
Tetrahydrofuran	109-99-9	THF	Flammable liquid: 2, H225 Eye irritation: 2, H319 STOT SE: 3, H335
Dimethylsulfoxide	67-68-5	DMSO	Not classified
N-methylacetamide	79-16-3	NMAc	**Repr. 2, H360d *****
Formamide	75-12-7		**Repr. 2, H360d *****
2-Furaldehyde	98-01-1		Acute Tox. 3 *, H301/331 Acute Tox. 4 *, H312 Skin Irrit. 2, H315 Eye irritation: 2, H319 STOT SE: 3, H335 **Carc. 2, H351**

Regarding the desirability of various solvents, one may take into account also ecological and health effects, the latter e.g. orientating on the pharmaceutical industry as pharmaceuticals are very strictly regulated.

Kerton, as already mentioned above, developed three solvent categories, i.e., preferred, usable and undesirable based on hazard profiles as described in table C8. The preferred solvents are classified as 'green' alternatives for DMF, see table C8. She also noted that few solvents are inherently green and most solvents can be handled safely in well designed plants with appropriate risk reduction measures in place (good recovery and recycle facilities) (Kerton, 2009).

Table C8: A green chemistry-based solvent selection guide distinguishing three categories being preferred, usable and undesirable according to Kerton, 2009).

Category	Substance
Preferred	water, acetone, ethanol, 2-propanol, ethyl acetate, isopropyl acetate, methanol, methyl ethyl ketone, 1-butanol, t-butanol
Usable	cyclohexane, heptane, toluene, methylcyclohexane, methyl t-butyl ether, isooctane, 2-methyltetrahydrofuran, cyclopentyl methyl ether, xylenes, dimethylsulfoxide, acetic acid, ethylene glycol

Category	Substance
Undesireable	pentane, hexane(s), di-isopropyl ether, diethyl ether, dichloromethane, dichloroethane, chloroform, dimethylformamide, n-methylpyrrolidone, pyridine, dimethylacetamide, acetonitrile, tetrahydrofuran, dioxane, Dimethyl ether, benzene, carbon tetrachloride

The European Medicines Agency prepared a guideline for residual solvents in medicines. They distinguish four categories, from solvents that should be avoided (class 1) to solvents with low toxic potential (class 3) and solvents for which no adequate toxicological data were found (class 4), see table C9. DMF was classified in class 2 (Solvents to be limited) (ICH, 2011).

Table C9: Classification of residual solvents in pharmaceuticals (ICH, 2011)

Class	Substance
Class 1	Benzene, Carbon tetrachloride, 1,2-Dichloroethane, 1,1-Dichloroethene, 1,1,1-Trichloroethane
Class 2	Acetonitrile, Chlorobenzene, Chloroform, Cumene1, Cyclohexane, 1,2-Dichloroethene, Dichloromethane, 1,2-Dimethoxyethane, N,N-Dimetylacetamide, N,N-Dimethylformamide, 1,4-Dioxane, 2-Ethoxyethanol, Ethyleneglycol, Formamide, Hexane, Methanol, 2-Methoxyethanol, Methylbutyl ketone, Methylcyclohexane, N-Methylpyrrolidone, Nitromethane, Pyridine, Sulfolane, Tetrahydrofuran, Tetralin, Toluene, 1,1,2-Trichloroethene, Xylene*
Class 3	Acetic acid, Acetone, Anisole, 1-Butanol, 2-Butanol, Butyl acetate, tert-Butylmethyl ether, Dimethyl sulfoxide, Ethanol, Ethyl acetate, Ethyl ether, Ethyl formate, Formic acid, Heptane, Isobutyl acetate, Isopropyl acetate, Methyl acetate, 3-Methyl-1-butanol, Methylethyl ketone, Methylisobutyl ketone, 2-Methyl-1-propanol, Pentane, 1-Pentanol, 1-Propanol, 2-Propanol, Propyl acetate
Class 4	1,1-Diethoxypropane, 1,1-Dimethoxymethane, 2,2-Dimethoxypropane, Isooctane, Isopropyl ether, Methylisopropyl ketone, Methyltetrahydrofuran, Petroleum ether, Trichloroacetic acid, Trifluoroacetic acid

Explanation:
Class 1 solvents in pharmaceutical products. (solvents that should be avoided)
Class 2 solvents in pharmaceutical products. (solvents that should be limited)
Class 3 solvents which should be limited by GMP or other quality based requirements. (Solvents with Low Toxic Potential)
Class 4 solvents. Solvents for which no adequate toxicological data was found

Generally, organic carbonates have low toxicities and environmentally friendly properties which makes them acceptable alternatives for standard organic solvents and valuable candidates to substitute polar, aprotic solvents such as DMF and NMP (Schäffner, 2010).

Taking into account the classification of the technically possibly suitable alternatives as compiled in Table C7, and the recommendations by Kerton and ICH (Tables C8 & C9), DMF cannot be reasonably replaced by most of the mentioned substances. NMP, HMPA, DMAc, HMPT, Benzene, Toluene, NEP, NMAc, Formamide, and 2-Furaldehyde are not suitable due to their classification as either Reproductive Toxicant or Carcinogen and/or Mutagen, as it is pointless to substitute DMF by another CMR substance.
Furthermore, both Acetonitrile and Tetrahydrofuran are listed as undesirable substance within the 'green' alternatives, and are mentioned as Class 2 solvent in pharmaceutical products, i.e. solvents which should be limited. Consequently, those solvent should not be considered as suitable alternative in terms of their intrinsic hazard, too.

So, the only remaining substances are DMSO and MEK. The latter, however, also bears a certain hazard, as it is classified as flammable liquid, Eye irritant class 2 and STOT SE 3, according to ECHA's

dissemination website due to effects on the central nervous system. In consequence, regarding worker and consumer protection, DMSO should be the preferred alternative. Nevertheless both solvents are already used in a number of applications, which are certainly posing suitable alternatives for DMF. However, those solvents are not generally able to replace DMF in all its applications.

DMSO consequently should be selected as substance as it is also a polar apriotic solvent, it was mentioned as alternative to DMF for most applications, and has most use and hazard information available which will be described in more detail below. Industry also indicated that DMSO is the main long-term alternative to DMF available on the market. Whilst DMSO certainly is not a drop-in substitute for all applications, it has a broad spectrum of uses in which it could replace DMF, significantly reducing environment and/or health risk

Today it does not seem to be one single alternative that can replace DMF for all its uses, indicating that an authorization process would clearly eliminate several applications as authorization would make many processes no economically feasible anymore. However, within the above mentioned substances covering the major amount of the applications of DMF, and mainly due to classification issues, it became evident that DMSO is the only alternative relevant for further assessment, which will be performed.

C.2.1 Availability of DMSO

According to the summary conclusions of SIAR (SIDS Initial Assessment Report), “the worldwide consumption of DMSO is estimated for the year 2004 between 30,000 T and 40,000 T. The production sites are located, one in Europe, one in Japan, one in the United States and several sites (3-4) of smaller size in China. With its high polarity combined with a high electric constant, DMSO is known to be an excellent solvent for polar or polarizable organic compounds, and also many acids, alkalis and mineral salts. DMSO is used industrially, and not exclusively, as a reaction, polymerization, clean-up and pharmaceutical solvents, paint and varnish removers, analytical reagent, in the manufacture of synthetic fibers, industrial cleaners and pesticides and in the electronic industry. DMSO is also used as a preservative for organ transplantation and for the treatment for the symptoms of interstitial cystitis. There is a well-known phenomenon of use of DMSO by patients for other than the treatment of interstitial cystitis purposes, primarily to treat sprains, bruises, minor burns and arthritis. It should be noted, that only a medical purity grade DMSO is safe, and the technical grade DMSO should not be used for the curative dermal applications. In addition, DMSO enhances the permeability of skin to other substances. Fifty percent of the DMSO applications are in the pharmaceutical and agrochemical industries, 25% in the electronics, 10% in fine chemistry and 15% in other applications” (OECD, 2008).

C.2.2 Human health risks related to DMSO

There is no harmonized classification according to Regulation (EC) No 1272/2008 for DMSO (ECHA, 2014b). An extensive dataset is available for DMSO regarding its physico-chemical, environmental and toxicological properties (OECD, 2008). The available data demonstrate that DMSO is of low concern for the environment and the human health, at least on its own. In combination with other substances, however, it may pose a certain risk. Due to its oxidizing properties, corrosions and exothermic reactions leading to explosions may occur, e.g. in combination with caustic potash which led to the explosion on 8 July 1999 at Bayer AG in Wuppertal-Elberfeld. Furthermore, DMSO exhibits a percutaneous carrier effect enableing other substances to penetrate the skin more easily in the presence of DMSO (Petereit, 2014).

In the following subchapters the main toxicological aspects of DMSO are described according to the SIDS initial assessment profile of DMSO (OECD, 2008).

C.2.2.1 Toxicokinetic behaviour of DMSO

"No data is available on the absorption of DMSO by inhalation exposure. However, its physico-chemical properties (low molecular size, high polarity and water solubility) suggest that DMSO is significantly absorbed by the inhalation route. DMSO appears to be readily absorbed through the skin. An *in vitro* permeability rate of 176 g/m² per hour has been reported for human skin. Maximal serum concentration of DMSO occurred at 4 to 8 hours following skin contact in humans, and at 2 hours in rats. DMSO is also well absorbed after oral exposure. Peak plasma concentration of DMSO was attained at 4 hours after oral dosing in humans and at 0.5 hours in rats. DMSO is widely distributed to all body tissues. Higher concentrations of DMSO were found in the kidney, spleen, lung, heart and testes of rats given an oral dose, while higher levels were noted in the spleen, liver and lungs following a dermal dose. In humans, the plasma DMSO clearance half -life was about 11 to 14 hours, and 20 hours after dermal and oral dosing, respectively. A shorter clearance half -life of 6 hours was observed in rats after both routes of exposure. Metabolism of DMSO takes place primarily in the liver and kidneys. The principal metabolite is dimethyl sulfone ($DMSO_2$). Peak plasma levels of $DMSO_2$ in humans were observed at 72 to 96 hours after dosing, and then declined with a half-life of about 60 to 72 hours. DMSO is excreted unchanged or as the metabolite $DMSO_2$ in the urine. In the human, about 13 and 18% of a dermal dose, and 51% and 10% of an oral dose were accounted for by urinary excretion of DMSO and $DMSO_2$, respectively" (OECD, 2008).

C.2.2.2 Acute Toxicity of DMSO

"DMSO is of low acute toxicity. In non-GLP studies, LD50 in rats are generally higher than 20,000 mg/kg bw and 40,000 mg/kg bw by the oral and dermal routes, respectively. In an acute inhalation study performed following the OECD TG 403, the LC50 in rats was higher than 5000 mg/m³ for a 4-hour exposure" (OECD, 2008).

C.2.2.3 Irritating Properties of DMSO

"A skin irritation assay performed in rabbit according to the OECD TG 404 revealed no more than a very slight or well-defined erythema, which disappeared in 3 days. In humans, repeated application of DMSO solution for up to several months could induce transient erythema, burning, stinging and itching, which returned to normal after discontinuation of treatment. In one study in humans, occlusive exposure to DMSO caused cell death of the outer epidermis, followed by rapid regeneration. DMSO is slightly irritating for the eye. In studies performed following the OECD TG 405 or the EEC method B.5, a slight to moderate conjunctival irritation, which cleared in 3 days, was observed in the eyes of rabbits. A repeated instillation (100% DMSO, 3 times/day for 6 months) in the eyes of rabbits induced only a temporary lacrimation but did not show any changes in the iris, cornea, lens, retina, conjunctiva and lids. In humans, the instillation of solutions containing 50 to 100% DMSO has caused transient sensation of burning which was reversible within 24 hours" (OECD, 2008).

C.2.2.4 Sensitizing effects of DMSO

"DMSO is not a skin sensitizer. Sensitization tests performed in guinea pigs and mice following methods comparable to the OECD TG 406 were uniformly negative. A skin sensitization assay performed in humans was also negative" (OECD, 2008).

C.2.2.5 Repeated Dose Toxicity of DMSO

"DMSO is of low toxicity by repeated administration. According to the results of a 13-week inhalation toxicity study compliant with the OECD TG 413, the No Adverse Effects Concentration (NOAEC) for DMSO could be established at *ca.* 1000 mg/m³ for respiratory tract irritation and *ca.* 2800 mg/m³ (the highest concentration tested) for systemic toxicity. Other non-guideline repeated dose toxicity studies performed by different routes of administration and with several mammalian species have also shown that DMSO produced only slight systemic toxicity. With the exception of a decrease of the body weight gain and some hematological effects (which could be secondary to an

increased diuresis) at very high dose levels, the most common finding observed in these studies is changes of the refractive power of the lens. These ocular changes were observed following repeated oral application of DMSO at doses of around 3000 mg/kg bw/d in rats for 18 months and 1000 mg/kg bw/d in dogs for 2 years. Following repeated dermal application, the same effects were observed at doses of around 1000 mg/kg bw/d in rabbits for 30 days, in dogs for 118 days and in pigs for 18 weeks. Similar ocular changes were not observed in monkeys following dermal application at doses of up to 9000 mg/kg bw/d for 18 months (dose levels that caused marked ocular toxicity in sensitive species). Clinical signs of systemic toxicity and the alterations of the lens were also never observed or reported in clinical and epidemiological studies performed in humans, even after exposure to a high dose level (1000 mg/kg/d for 3 months) or for a long period of time (up to 19 months). Overall, primates appear to be much less sensitive to DMSO ocular toxicity, and the ocular changes observed in rats, rabbits, dogs or pigs are not considered relevant for human health. Then, it is possible to estimate that the No Observed Adverse Effect Levels (NOAELs) by oral or dermal routes would be close to 1000 mg/kg bw/d" (OECD, 2008).

C.2.2.6 Mutagenicity of DMSO

"In studies performed with methods compliant or comparable to OECD guidelines, no genotoxic activity was observed for DMSO in gene mutation assays in *Salmonella typhimurium,* an *in vitro* cytogenetics assay in CHO cells and an *in vivo* micronucleus assay in rats. With few exceptions, a large battery of additional *in vitro* and *in vivo* non-guideline studies confirmed the lack of genotoxic potential" (OECD, 2008).

C.2.2.7 Reproductive Toxicity of DMSO

"DMSO is not a reproductive toxicant. In a Reproduction/Developmental Toxicity Screening Test performed following the OECD TG 421, the NOAEL for parental toxicity, reproductive performance (mating and fertility) and toxic effects on the progeny was considered to be 1000 mg/kg/day. In addition, no effect was observed on the estrus cycle, the sperm parameters (count, motility and morphology) and the reproductive organs of male and female rats after a 90-day inhalation exposure to DMSO concentrations up to 2800 mg/m³. In developmental toxicity studies performed according to the OECD TG 414, oral administration of DMSO to pregnant female rats or rabbits during the period of organogenesis was not teratogenic. The NOAELs for maternal toxicity were 1000 and 300 mg/kg bw/d in rats and rabbits, respectively, and the NOAELs for embryo/foetotoxicity were 1000 mg/kg bw/d in both species" (OECD, 2008).

C.2.2.8 Conclusion on Human Health Effects of DMSO

DMSO has limited human health toxicity as indicated by the absence of self-classification in the majority of notifications and based on the available summaries. It should be noticed, however, that DMSO acts as a skin penetration enhancer for many substances and the traditional rubber handgloves do not - in general – provide the desired protection. Consulting ECHA's dissemination website (http://apps.echa.europa.eu/registered/data/dossiers/DISS-828e0a4f-03e4-1d1a-e044-00144fd73934/AGGR-c28906f8-9242-4c0b-98e0-97def35089b6_DISS-828e0a4f-03e4-1d1a-e044-00144fd73934.html#AGGR-c28906f8-9242-4c0b-98e0-97def35089b6), the derived no effect levels (DNELs) are:

Table C10: Longterm DNELs for DMSO, taken from ECHA's dissemination website 15 August 2014:

	Systemic Effects			**Local Effects**	
	Oral	**Dermal**	**Inhalation**	**Dermal**	**Inhalation**
Workers		200 mg/kg bw/day	484 mg/m³	n/a	265 mg/m³
General Population	60 mg/kg bw/day	100 mg/kg bw/day	120 mg/m³	n/a	47 mg/m³

Comparing this information with the data provided on DMF in chapter B, DMSO has no CMR properties and is of lower toxicity to human health.

C.2.3 Environment risks related to DMSO

"DMSO is a liquid (density 1.1) with no color but in some cases a light characteristic sulfur odor due to traces of the raw material dimethyl sulfide. DMSO has a melting point of 18.5°C and a boiling point of 189°C (at 1,013 hPa). Its log Kow is of –1.35 (measured). DMSO has a vapour pressure of 0.81 hPa at 25°C and a Henry law's constant of $1.17*10^5$ $mol.kg^{-1}.atm^{-1}$. DMSO is miscible in all proportion with water and with most of the common organic solvents such as alcohols, esters, ketones, ethers, chlorinated solvents and aromatics. DMSO is stable in water and is not expected to volatilize. DMSO Log Koc is estimated to be equal to 0.64. This value suggests that DMSO is mobile in soil. DMSO is not expected to adsorb to suspended solids, sediments and soils. In atmosphere, DMSO is not susceptible to direct photolysis by sunlight. Calculations indicate DMSO half-life values, for reaction with OH radicals, from *ca* 2 to 6 h.
Distribution modeling using Mackay Fugacity model Level III, for equal release in the environment (*i.e.* 1000 kg/h), indicates that the main target compartment will be soil (60.4%) and water (39.5%) with the remainder partitioning between air (0.0334%) and sediment (0.0723%). DMSO is not expected to bioaccumulate in the aquatic environment based on a measured bioconcentration factor lower than 4. One readily biodegradation test performed following the norm AFNOR NF T 90-312 concluded that DMSO is readily biodegradable. Nevertheless, based on literature data and weight-of-evidence approach, better expectation is to consider DMSO as inherently biodegradable. For instance, 500 mg/L DMSO were entirely biodegraded within *ca*. 37h with aerobic settling sludge obtained from the activated sludge process at an opto-electronic plant, under optimized pH/temperature conditions. In a test report following OECD TG 303A, it has been validated that more than 90% DMSO was biodegraded at a concentration of 65 mg/L after 32 days of exposure. Acute toxicity studies, carried out for some of them according to guidelines similar to OECD guidelines, reveal 48-hour EC50's ranging from 24,600 to 58,200 mg/L for daphnid (*Daphnia magna*) and 96-hour LC50's ranging from 32,300 to 43,000 mg/L for fish according to the species considered (*eg. Ictalurus punctatus, Lepomis cyanellus)*. Modeling calculation for algae indicates 96-hour EC50 value of about 400 mg/L. On this basis DMSO can be considered non-toxic for aquatic compartment" (OECD, 2008).

C.2.4 Technical and economic feasibility of DMSO

C.2.4.1 Technical feasibility

DMSO is highly stable at temperatures below 150° C. For example, holding DMSO at 150° C for 24 hours, one could expect a loss of between 0.1 and 1.0%. It has been reported that only 3.7% of volatile materials are produced during 72 hours at the boiling point (189° C) of DMSO. Above, decomposition takes place, following a time-temperature function that can be accelerated by the addition of acids and be retarded by some bases. The decomposition, catalysed by acids, can even be relevant at lower temperatures. DMSO can react vigorously and even explosively with strong oxidizing agents, such as magnesium perchlorate and perchloric acid. These characteristics may limit application of DMSO (Gaylord Chemical Company, 2003).

Solvent in SN reactions

DMF is widely used as solvent in the synthesis of chemicals, especially involving SN2 and SNAr reactions. Those include applications in the synthesis of Fine Chemicals, Pharmaceuticals, or Plant Protection Products. Aprotic solvents are frequently used for SN2 displacement reactions, where they stabilize the charge-separation that occurs in the transition state. Hence, the group of polar aprotic solvents can generally not be replaced by other solvent types, and alternatives must be searched within this group, which also DMSO belongs to.
DMSO is a good solvent for SN2 displacements, although the yield is lower resulting in a higher use of

chemicals and increasing waste streams. It is difficult to regenerate large quantities of DMSO due to thermal instability and there have been reported accidents in the literature. Unfortunately it is incompatible with very strong nucleophiles or bases as well as not suitable for reactions at low temperatures due to its rather high melting point of 18.5°C. Also its high boiling point poses a big drawback because it is so difficult to remove by evaporation. Especially in the field of Plant Protection Products this would result in a widespread exposure of DMSO on the crops, environment and man.
So in general, DMSO may serve as substitute, but its application is strongly dependent on specific use. Also, in case of Pharmaceuticals and Plant Protection Products, an exchange of the solvent will trigger high costs regarding development and regulatory compliance, as here every variation of the manufacturing conditions may trigger a new application at the respective governmental body.

Butadiene production / Extraction solvent

No information was available on the use of DMSO in Butadiene production, and there are no data that show it has already been applied in this area. Regarding its use as extraction solvent in general, it should be general possible to use it in specific processes due to its general solvate power. However, this application is strongly dependent on the respective analyte.

Transport of Acetylene Gas

DMSO has been assessed as possible substitute for DMF as solvent in the transport of acetylene gas. Relevant for this application is a sufficient solvate power, a low vapour pressure in order to avoid impurities in the effusing gas as well as a low melting point in order to allow a transport without freezing of the solvent even at very low ambient temperatures, e.g. during winter. Although DMSO has even a lower vapour pressure (0.6 hPa at 20°C) than DMF (3.6 hPa at 20°C), its high freezing point of 18.5% eliminates it as a potential substitute.

Polymers: Polyurethane Production, Use for Artificial leather, Membranes Production, Coatings Production

It is well documented that, besides DMF, DMSO is also a good solvent for many polymers and is often used in preparing polymer solutions; it bears a solvating capability comparable to DMF. Nevertheless it must be mentioned that polyurethane production, or in the production of polymers in general, remarkable differences in the performance of the final polymer / coating / membrane can result from the application of different solvents. Also, e.g. in the coagulation process in the production of artificial leather, currently no suitable alternative is known. In consequence, the suitability of DMSO is very dependent on the required final polymer. DMSO is additionally is affected by important limits as the high melting point at 18°C, this feature excludes the use in application processes for Polyurethane elastomers because no any of the existing plants are able to handle solid products at room temperature. Due to its high boiling point (189°C) it requires higher operating temperatures and hence more energy. Most available plants are incapable of handling technological processes at this elevated temperatures, and the removal by drying of the final PU product is rather difficult because of its high boiling point and low vapour pressure. Furthermore, DMSO is also corrosive and this is another excluding condition for the existing plants in application, as this would require new ovens to be build from stainless steel. For e.g. clearcoats it was considered unsuitable i.a. because of the colour stability of the final product and difficulties in process handling due to its hygroscopic behaviour.

Polymers: Polyurethane curing and removal

For i.a. recycling issues, the cured polyurethane coating must also be removable. DMSO is no suitable alternative here as it lacks a similar performance.

Fiber Production

DMF is widely used as a spinning solvent in fiber production, the most common fibers are

polyacrylonitril (PAN) fibers. Either the polymer solution is precipitated in a water bath (wet-spinning process) or the fibers are spun by evaporation of the solvent after leaving the spinnerette (dry-spinning process).
Relevant for the properties of the final fibers is i.a. the viscosity of the solvent with respect to the concentration of the polymer in solution. DMF solutions exhibit a way lower viscosity than DMSO solutions. This is connected to the effective speed and achievable degree of polymerization. At first sight, DMSO seems favourable compared to DMF regarding both the effective speed and diminished chain formation constant. Via an adequate choice of the polymerization conditions these difficulties however can be compensated and the advantages of DMF can be utilized, such as the lower viscosity of the spinning solution with comparable polymer concentration, as already said, the diminished tendency for coagulation and lower evaporation heat. The latter is relevant for the possibility to remove the solvent from the polymer solution / fiber. Since DMSO has a higher boiling point and lower vapour pressure as DMF, as already described above, larger amounts of DMSO are expected to remain in the final fiber, resulting in an enhanced exposure of the general population as well as an undesirable smell of the final product.
In summary, DMSO is not an adequate surrogate for DMF in fiber production.

Medical Devices (MD): Polyurethane in MDs, PU and other polymer films in wound dressings

In general, no detailed information is available regarding the suitability of DMSO as a replacement in medical devices. It should however be kept in mind that the amount of residual process solvent needs to be minimized. Using DMF, the residual amounts are negligible, which is only achievable because DMF has a rather low boiling point of 152-153°C at 1013 hPa. DMSO has a way higher boiling point, as already outlined above, the solvent from the production process could not be removed by simple drying, which would lead to a rather high amount of remaining solvent in the wound dressing. Due to its low molecular weight and dipolar aprotic nature, an absorption of the remaining solvent is given, which should be avoided. Hence, DMSO is no suitable alternative here.

Pharmaceuticals

DMSO was, among others, classified by ICH as a class three substance, i.e. a solvent with low toxic potential which should be limited by GMP or other quality based requirements (ICH, 2011). DMSO is already applied in pharmaceutical industry, but if this considers the whole range of products is not evident. For many other applications DMSO has been indicated as a potentially reactive chemical and that thermal instability can be induced by a range of chemicals / impurities. Also, regarding its physico-chemical characteristics being different from DMF, it may not be a suitable alternative at all, as already outlined above.

C.2.4.2 Economic feasibility

The prices for DMSO are in the same range as for DMF. Even the costs may vary from country to country or region to region slightly, the substitution of DMF by DMSO is not coupled to remarkable cost differences. Thus, substitution of DMF by DMSO is only based on the technical feasibility and the required product properties. During the evaluation of data for this report it became clear that most involved companies have been looked for DMF alternatives but did not identify DMSO as an appropriate substitute in most applications. However, where possible, DMSO has already been applied in some processes and applications, such as the petrochemical industry, non-wire coatings, within photoresist strippers. Within membrane production and pharmaceuticals it seems to have been applied on a limited scale.

Regarding Pharmaceuticals or other highly regulated applications, an issue concerning costs is that regulatory implications that may be associated with changing the solvent used in any stage of a commercial manufacturing process that is registered with the appropriate regulatory health authorities may invariably require extensive redevelopment of processes and associated interaction/authorisation from health authorities in order to ensure product quality, efficacy and patient safety.

C.2.5 Conclusion on DMSO

The use of DMSO as alternative for DMF has been described by industry for a limited number of applications. It is believed that due to both economic and toxic considerations industry would have replaced DMF by DMSO if possible. Regarding the remaining uses of DMF as described in chapter B, it is considered that DMSO is not a technical feasible alternative for all applications at this moment. As indicated earlier in this chapter, other solvents may be more feasible to replace DMF for specific applications.

The possible substitution of DMF by DMSO has been described, because DMSO is not classified as dangerous, contributes to the reduction of environmental and human health risks. For certain applications DMSO can definitely been used as described above. However, for other applications, different solvents have been preferred as possible alternatives, because of the limitations of DMSO. Amongst these, DMSO is able to dissolve and transport other substances trough gloves and skin and can be considered as a skin penetration enhancer. In addition due to the characteristic that industry claimed that DMSO is under specific conditions (above 150°C) thermal instable, the application remains – so far – limited.

D. Justification for action on a Community-wide basis

D.1 Considerations related to human health and environmental risks

As described in detail in section B and referring to information from ECHA (2012, 2014), Swedish Chemicals Agency (2012) and the registration dossier (2014), the main use of DMF (ca. 80%) is as a solvent in chemical synthesis of pharmaceuticals, agrochemicals and fine chemicals, and in addition, used in electronic industry and as a solvent in the synthesis of artificial fibers or artificial leather. The pharmaceutical industry also uses DMF to sterilize powders and ampules and in various quality control applications. The 20% remaining applications are assumed to be used as intermediate, as laboratory chemical, as cleaning solvent and in formulations. The substance is potentially used in all Member States while the use is expected to be higher in some Southern EU countries. The Tier 2 Exposure Assessment and the Chemical Safety Assessment conducted by the Lead Registrant of DMF identified for some processes occupational exposure which might lead to risks. Furthermore, the German "Institut für Arbeitsschutz und Arbeitsmedizin der deutschen Gesetzlichen Unfallversicherung (IFA)" has published measurement data for several branches (2012). 37 branches and 71 workplaces have been examined and 13% of the reported measurements were exceeding the indicative OEL, but this was not based 8 hours average working exposure. Furthermore, ECHA's Draft Recommendation Document (2012) identifies use of DMF in mixtures such as sealants, strippers, paints, coatings, mastics or glue as source for potential significant exposure of workers, especially professionals, within the EU.

DMF is not supposed to be a component of the final product although some traces may still remain in the article. This was confirmed by ZUTTER (2011), who investigated and measured DMF concentrations in PU-coated gloves, in uncoated fabrics and knitted welt. None of the tested gloves complied with the German limit value for gloves of 10 mg/kg (TRGS 401). No-name Asian imports had concentration of up to 3.600 mg/kg. Moreover, Greenpeace (2014) published a study concerning hazardous chemicals found in World Cup merchandise. All 21 pairs of football boots were tested positive on DMF residual content. 19 of these contained levels above the 10 mg/kg limit set by the German Committee on Hazardous Substances (AGS). All of the football boots were manufactured in South Asia (9 in China, 8 in Indonesia, 2 in Vietnam and 1 in Cambodia), with the exception of one pair, which was manufactured in Bosnia.

Consequently, there is clear evidence that human health risks are potentially arising from some industrial processes and industrial and consumer articles at EU-wide scale.

D.2 Considerations related to internal market

DMF and products (mixtures) containing it are manufactured, imported and used in the EU. They are freely traded in all Member States. EU-wide measures, like a restriction, would avoid a distortion of the internal EU-market, which might arise in case national measures would be implemented. Acting at EU-level would therefore ensure a "level-playing field for all producers and importers. From a legal perspective the principle of the free movement of goods has been a key element in creating and developing the internal EU market (Articles 28–30 of the EC Treaty). Currently, various national OELs exist at Member State level, ranging from 15 – 30 mg/m^3. 6 Members States have not updated their national OELs according to the EUs indicative OEL since 2009 (Bulgaria, Czech Republic, France, Greece, Portugal and Sweden). Thus, to ensure the same level of protection of human health across the EU and to enhance the good functioning of the internal market, action needs to be taken on an EU-wide

basis. An EU-wide restriction also provides a clear message on the status of the requirements and is easy to communicate to non-Community suppliers.

D.3 Other considerations

Due to its properties of being toxic to reproduction (Cat. 1B), ECHA's Member State Committee (MSC) agreed on 29th of November 2012 to include DMF in the Candidate List for possible Authorisation requirements under REACH. On the 24th of June 2013 ECHA published a document developed in the context of ECHA's 5th Recommendation for DMF's inclusion in Annex XIV (Authorisation List). Hence, actions for this substance are already taken on an EU-wide level. Consequently, alternative measures should equally be taken on Community-wide basis.

Furthermore, two potential substitutes of DMF (DMAC and NMP, see Section C) meet as well the criteria for classification as toxic for reproduction (Category 1b) and therefore qualify for inclusion in REACH Annex XIV. DMAC and NMP are both in the SVHC process. For NMP (N-Methyl-2-pyrrolidone) the Netherlands has submitted a Restriction Proposal (RIVM, 2013). Concerning DMAC (N,N-Dimethylacetamide) and its inclusion into Annex XIV, the Commission stated in its very recent Regulation No 895/2014 of 14th August 2014 the following:

"DMAC has similar intrinsic properties to those of N-Methyl-2-pyrrolidone (NMP) and both substances may be considered as potential alternatives for some of their major uses. Currently the chemical substance NMP is the subject of a restriction procedure in accordance with Article 69 of Regulation (EC) No 1907/2006. In view of the similarities of the two substances, both regarding their intrinsic properties and their industrial applications, and in order to ensure that a consistent regulatory approach is warranted, the Commission considers it appropriate to postpone the decision on the inclusion of DMAC in Annex XIV".

Therefore, the Dossier Submitter (DS) suggests that for DMF a consistent approach on EU-wide level is warrented too.

D.4 Summary

The main reason for acting on a Community-wide basis is the protection of human health from the adverse effects of DMF due to its reprotoxic (Category 1B) properties. There is strong evidence, that in some industrial settings occupational exposure exists and that consumers are exposed through articles containing residual content of DMF up to gram-level. According to the EU's Treaty, free movement of goods need to be guaranteed in order not to distort the internal market. Therefore, acting on a Community-wide basis ensures equal treatment of both - EU producers and importers, gives a clear message to non-Community suppliers and provides a "level playing field" and equal protection of human health across the EU.

E. Justification why the proposed restriction is the most appropriate Community-wide measure

E.1 Identification and description of potential risk management options

E.1.1 Risk to be addressed – the baseline

The main reason for the need to act on a Community-wide basis is the protection of human health from the adverse effects of DMF due to its reprotoxic (Category 1B) properties. There is strong evidence that DMF is potentially used in all EU Member States and that in some industrial settings occupational exposure may exist. Moreover, it is demonstrated, that consumers can be exposed through articles containing residual content of DMF, up to gram-level. The objective is to prevent or to adequately control exposure of DMF to workers and to the general public in order to prevent ill health. Worker exposure information in the registration dossier and data on residual content of DMF in articles indicate clear evidence, that risks are arising from some uses and that consumer exposure cannot be ruled out and thus risks need to be controlled.

Therefore, the Restriction Proposal is targeted to the critical uses of DMF in industrial settings, to the "risky" uses in professional applications and to the exposure of workers and consumers through unreasonable residual content of DMF in articles. The primary routes of industrial exposure to DMF are skin contact and inhalation. No specific risks have been identified concerning the environment compartment.

The Risk Assessment in Section B of this dossier includes the details.

E.1.2 Options for restrictions

In most cases where a concern related to a substance has been identified, there will be several options for addressing this concern. The different legislative measures that may be used all have different strengths and weaknesses which will vary depending on the case. Due to the fact that DMF is already included in the Candidate List and subject to strict Classification & Labelling requirements (CHL), beside Authorisation (see E.1.3) only the following risk management options (RMOs) have been considered:

<u>RMO 1 – Complete restriction</u>

The first RMO is the total ban for placing on the market and use of DMF for all applications in the EEA.

<u>RMO 2 – Partial Restriction 1</u>

This option is a combination of the following measures:

a. Harmonization of national OELs (currently there exist various national OELs between 15 and 30 mg/m^3) in practice: DMF shall not be manufactured and used by professional or industrial workers, unless the 8-hour TWA exposure will remain below 15 mg/m^3 and the 15 min peak exposure (STEL) remains below 30 mg/m^3. According to Article 2(4) of REACH, employers and manufacturers must be compliant with both chemical and occupational legislations.

b. Dermal exposure is avoided by preventative measures to comply with the DNEL for dermal exposure.

c. The professional use of DMF is restricted to professional laboratories only, as laboratory use already fulfils the criteria of 'safe use' (RCR<1, see section B).

d. Articles may not be placed on the market if they or parts thereof, contain DMF in concentrations higher than 0.1% by mass (w/w). The concentration limit should be applicable for each individual part of the article.

RMO 3 - Partial Restriction 2

This option is a combination of the following measures:

a. Harmonization of national OELs (currently there exist various national OELs between 15 and 30 mg/m^3) in practice: DMF shall not be manufactured and used by professional or industrial workers, unless the 8-hour TWA exposure will remain below 15 mg/m^3 and the 15 min peak exposure (STEL) remains below 30 mg/m^3. According to Article 2(4) of REACH, employers and manufacturers must be compliant with both chemical and occupational legislations.

b. Dermal exposure is avoided by preventative measures to comply with the DNEL for dermal exposure.

c. The professional use of DMF is restricted to professional laboratories only, as laboratory use already fulfils the criteria of 'safe use' (RCR<1, see section B).d. Articles may not be placed on the market if they or parts thereof, contain DMF in concentrations higher than 0.3% by mass (w/w). The concentration limit should be applicable for each individual part of the article.

RMO 4 - Partial Restriction 3

This option is a combination of the following measures:

a. Harmonization of national OELs (currently there exist various national OELs between 15 and 30 mg/m^3) in practice: DMF shall not be manufactured and used by professional or industrial workers, unless the 8-hour TWA exposure will remain below 15 mg/m^3 and the 15 min peak exposure (STEL) remains below 30 mg/m^3. According to Article 2(4) of REACH, employers and manufacturers must be compliant with both chemical and occupational legislations.

b. Dermal exposure is avoided by preventative measures to comply with the DNEL for dermal exposure.

c. The professional use of DMF is restricted to professional laboratories only, as laboratory use already fulfils the criteria of 'safe use' (RCR<1, see section B).

d. Articles may not be placed on the market if they or parts thereof, contain DMF in concentrations higher than 1.5% by mass (w/w). The concentration limit should be applicable for each individual part of the article.

RMO 5 – Targeted Restriction

For the uses/mixtures/articles for which alternatives appear to be readily available, the use of DMF is banned (e.g. paints; glue, paint stripper; spraying; hand mixing etc.)

E.1.3 Other Union-wide risk management options than restriction

Other non-REACH RMOs were not found completely suitable and efficient, because the existing non-REACH legal requirements did so far not provide adequate control for all risks to be addressed (section E.1.1).

Under REACH, another mechanism for limiting the use of harmful substances is Authorisation (Title VII). Authorisation is applicable to DMF as it has been identified as Substances of Very High Concern (SVHC) according to REACH Article 57(c) and was placed on the Candidate list for Authorisation in 2012. Hence, Authorisation will be assessed as second risk management option (RMO6) in E2.

E.2 Assessment of risk management options

In Chapter F (Socio-Economic Analysis, SEA) a more elaborated analysis of the two here briefly described RMOs can be found that further substantiates the argumentation given in this section.

E.2.1 Restriction option 1: Complete Restriction

See section E.1.2 for an outline of the proposed restriction.

E.2.1.1 Effectiveness (risk reduction capacity and proportionality)

Risk reduction for industrial and professional uses within the EU can be ensured (respective RCRs will decrease to zero) with this option, but the risks will only be shifted outside EU and revert due to import of articles containing DMF from non-EU countries. Hence, this option is considered not to be proportional (further explanation of the proportionality can be found in section F.6.3), as most of the users of DMF will find themselves forced to relocate or even terminate their business in case of a full ban of DMF.

E.2.1.2 Practicality (implementability, enforceability, manageability)

It is very difficult to substitute DMF and alternatives or techniques for these uses are currently not known, as many other available aprotic solvents have the same intrinsic properties with regards to reproductive toxicity as DMF (e.g. DMAC and NMP). Due to the absence of suitable alternatives implementability is clearly lacking and as long as a suitable (less harmful) alternative is not available, the total ban of DMF as aprotic solvent used by different industry sectors could not result in a benefit for human health.

E.2.1.3 Monitorability

Regarding monitorability, there are no specific concerns as this can be done through enforcement.

E.2.1.4 Overall assessment of Restriction Option 1

The risk reduction capacity of this RMO is limited: although reduction of risk for industrial and professional uses within the EU can be ensured, the problem will only be shifted outside EU, where it cannot be addressed with this option resulting even in an increase of health risks due to increased imports from outside EU with no control on origin or quality.

Regarding enforceability and monitorability there are no substantial differences to the other RMOs, but the practicability of this option is lower, as implementability is clearly lacking due to the absence of suitable alternatives.

According to the comments received during the consultation process, the following consequences will

be expected for the different industry sectors (more detailed information can be found in section F.4):

- Industrial gas industry: The application of RMO 1 to the industrial gases sector would lead to a social loss of **'Confidential information'**.
- Fiber industry: RMO 1 would likely have very severe impacts on the sector, as they would lead to a **'Confidential information'** of manufacturing of man-made fibers in the EEA. Stated in numbers, this RMO would represent at least **'Confidential information'** in identified monetary impacts. In the worst case, these impacts would represent **'Confidential information'**.
- Coating textile industry: A complete restriction of DMF would represent at least **'Confidential information'** in identified monetary impacts. In the worst case, these impacts would represent **'Confidential information'**.
- Pharmaceuticals sector: This sector provided limited information regarding potential effects of analysed RMOs. Nevertheless, it shows that a complete restriction would likely force the responding companies to move manufacturing and laboratory operations using DMF to non-EU countries and/or outsource these activities to companies outside the EU. **Confidential information**.
- Other industries: For some industries (agrochemicals, fine chemicals, phenolic resins, medical devices, sport industry, chemical industry and pigments-dyes), drawing general conclusions was not possible, as too few answers to the questionnaire were received. Overall, it only can be concluded that a complete restriction would lead to **'Confidential information'** in different sectors in the EEA.

E.2.2 Restriction option 2: Partial Restriction 1

See section E.1.2 for an outline of the proposed restriction.

E.2.2.1 Effectiveness (risk reduction capacity and proportionality)

Effectiveness is defined such as the RMO must be targeted at the effects or exposures that cause the identified risks, capable of reducing these risks to an acceptable level within a reasonable period of time, and proportional to the risk (ECHA, 2007). Due to the fact that there are no alternatives available that can replace DMF for all its uses (see section C.2), the proposed restriction is considered to be the most appropriate measure from a risk reduction capacity perspective, as it is clearly targeted to the identified risks and also addresses risks that could not be controlled through the authorisation process:

- Professional users in the non-chemistry sectors potentially using mixtures of DMF as strippers, paints etc. can be addressed directly (as ECHA claims to have identified a risk arising from non-registered uses.
- Potential risk(s) to the consumer coming from DMF in imported articles can be addressed by the restriction route as well.

In summary, this option provides more legal certainty and is expected to result in a complete risk reduction of DMF not only for industrial and professional uses (registered and non-registered), but also for consumers of imported articles. The expected risk reduction is further explained in section F.1.3.

The proposed restriction is targeted to the identified risks and does only affect uses or actors in the supply chain which are associated with the identified risks. Based on the results of the consultation process (detailed information on consultation can be found in Section G), it can be concluded that this RMO seems to give a good balance between costs and benefits, as wider socio-economic effects are avoided and the risk reduction of this scenario is substantial because risks will be reduced where this is

necessary). Further explanation of the proportionality of this RMO is given in section F.6.3.

E.2.2.2 Practicality (implementability, enforceability, manageability)

According to ECHA (2007), practicality means that the proposed restriction must be implementable, enforceable and manageable.

“Implementability” implies that the actors involved have to be capable in practice to comply with the restriction. To achieve this, the necessary technology, techniques and alternatives should be available and economically feasible within the timeframe set in the restriction. Specific industrial sectors (production of fine chemicals, pharmaceuticals and polymers) will have to put substantial effort in exposure reduction as a consequence of this RMO.

“Manageability” means that the proposed restriction or other considered RMOs should be manageable (taking into account the characteristics of the sectors concerned, for instance, the number of SMEs) and understandable to affected parties; the means of its implementation should be clear to the actors involved and the enforcement authorities and access to the relevant information should be easy. Furthermore, the level of administrative burden for the actors concerned and for the authorities should be proportional to the risk avoided.

RMO 2 seems to be implementable and manageable. The transitional period of two years that is proposed would, as indicated by stakeholder comments, allows sufficient time for implementation of the new requirements by e.g. technical adaptions or investments in new equipment to reduce exposure potential.

“Enforceability” is the ability of the authorities responsible for enforcement to check the compliance of the relevant actors with the proposed restriction. The restriction should be drafted in a way that allows the enforcement authorities to set up an efficient supervision mechanism(s). The resources needed for enforcement have to be proportional to the avoided risk. The restriction proposed is deemed to be enforceable:

- Analytical monitoring of DMF in workplace air and biological media is already widely performed using different standardised methods. For workplace air, methods of choice are high-performance liquid chromatography (HPLC), gas-liquid chromatography (GLC) or gas chromatography – mass spectrometry (GC-MS). Furthermore, detector tubes certified by US NIOSH, or other direct-reading devices calibrated to DMF can be used to easily determine workplace concentrations of the substance.

- For biological media, the metabolite most often analysed is N-methylformamide which can be determined by using several GC methods.

- The determination of DMF in some articles has also been investigated. For this purpose, the standardized method VDA 278 (Thermal Desorption Analysis of Organic Emissions for the Characterization of Non-Metallic Materials for Automobiles) was adequately adapted to DMF and specific articles. DMF residues in slimy toys have been analysed by Automated Thermal Desorption (ATD) using GC-MS while residues in gloves are described to be determined by Headspace GC-MS. Further adaptation of this standard procedure might be required to quantify DMF residues in other relevant articles, too.

E.2.2.3 Monitorability

Regarding monitorability, there are no specific concerns as this can be done through enforcement. Further, monitoring of exposure levels is already carried out under worker protection legislation and hence, it should be no problem to adopt similar activities.

E.2.2.4 Overall assessment of Restriction Option 2

All criteria used in the assessment of this RMO are fulfilled; all identified risks have been addressed. Although the risk is not completely removed as DMF will continue to be manufactured / used, it will be adequately controlled and all uses will be safe. The only problem might be the low limit for DMF in articles. Based on the comments received during the consultation process, the following consequences will be expected for the different industry sectors (more detailed information can be found in section F.4):

- Industrial gas industry: No significant impacts are to be expected, as European producers are currently using DMF under conditions that meet the standards corresponding to this RMO.
- Fiber industry: This RMO would lead to a **'Confidential information'** of the DMF-related activity, just like RMO 1 (**Confidential information**).
- Coating textile industry: Estimated impacts would be at least **'Confidential information'** in identified monetary impacts (**'Confidential information'** in the worst case).
- Pharmaceuticals sector: This sector provided limited information regarding potential effects of analysed RMOs. Nevertheless, it shows that they would continue using DMF under RMO 2.
- Other industries: For some industries (agrochemicals, fine chemicals, phenolic resins, medical devices, sport industry, chemical industry and pigments-dyes), drawing general conclusions was not possible, as too few answers to the questionnaire were received. Overall, it only can be concluded that adopting RMO 2 rather than a complete restriction would allow avoiding negative socio-economic impacts in several different sectors.

E.2.3 Restriction option 3: Partial Restriction 2

See section E.1.2 for an outline of the proposed restriction.

E.2.3.1 Effectiveness (risk reduction capacity and proportionality)

Risk reduction is comparable to RMO 2 and although there might be some minor differences on the benefit (risk reduction) and on the cost (economic effect) side, they will not change the conclusions on proportionality substantially. Further explanation of the proportionality of this RMO is given in section F.6.3.

E.2.3.2 Practicality (implementability, enforceability, manageability)

There should be no differences in regard to enforcability compared to RMO 2. Regarding implementability and manageability the slightly higher limit of DMF in articles would make compliance with these new limits easier for more actors in the supply chain (see section G & F for more details).

E.2.3.3 Monitorability

Regarding monitorability, there are no specific concerns as this can be done through enforcement. Further, monitoring of exposure levels is already carried out under worker protection legislation and hence, it should be no problem to adopt similar activities.

E.2.3.4 Overall assessment of Restriction Option 3

As for RMO2, also here all criteria used in the assessment of this RMO are fulfilled; all identified risks have been addressed. Nevertheless, concentrations above the trigger value 0.1 % w/w (i.e. 0.3 % w/w) bear a potential (unacceptable) risk for human health for some uses (e.g. gloves used by industrial workers) according to the human risk assessment (section B.9.3). Regarding implementability, the still

low limit for DMF in articles might be a problem. Based on the comments received during the consultation process, the following consequences will be expected for the different industry sectors (more detailed information can be found in section F.4):

- Industrial gas industry: No significant impacts are to be expected, as European producers are currently using DMF under conditions that meet the standards corresponding to this RMO.
- Fiber industry: With this RMO **'Confidential information'** of the DMF-based turnover would be terminated in the EEA and **'Confidential information'** employees would be laid off (loss of **'Confidential information'**).
- Coating textile industry: Estimated impacts would be at least **'Confidential information'** in identified monetary impacts (**'Confidential information'** in the worst case). In the worst case **'Confidential information'** of the industry's turnover would relocate and **'Confidential information'** would use an alternative substance. In the best case, **'Confidential information'** of industry's turnover would be affected.
- Pharmaceuticals sector: This sector provided limited information regarding potential effects of analysed RMOs. Nevertheless, it shows that they would continue using DMF under RMO 3.
- Other industries: For some industries (agrochemicals, fine chemicals, phenolic resins, medical devices, sport industry, chemical industry and pigments-dyes), drawing general conclusions was not possible, as too few answers to the questionnaire were received. Overall, it only can be concluded that adopting RMO 3 rather than a complete restriction would allow avoiding negative socio-economic impacts in several different sectors.

E.2.4 Restriction option 4: Partial Restriction 3

See section E.1.2 for an outline of the proposed restriction.

E.2.4.1 Effectiveness (risk reduction capacity and proportionality)

Risk reduction is comparable to RMO 2 and RMO 3; although there might be some minor differences on the benefit (risk reduction) and on the cost (economic effect) side, they will not change the conclusions on proportionality substantially. Further explanation of the proportionality of this RMO is given in section F.6.3.

E.2.4.2 Practicality (implementability, enforceability, manageability)

There should be no differences in regard to enforcability compared to RMO2 and RMO3. Regarding implementability and manageability the higher limit of DMF in articles would make compliance with these new limits possible for even more actors in the supply chain (see section G & F for more details).

E.2.4.3 Monitorability

Regarding monitorability, there are no specific concerns as this can be done through enforcement. Further, monitoring of exposure levels is already carried out under worker protection legislation and hence, it should be no problem to adopt similar activities.

E.2.4.4 Overall assessment of Restriction Option 4

As for RMO 2 & RMO 3, also here all criteria used in the assessment of this RMO are fulfilled; all identified risks have been addressed. Nevertheless, concentrations above the trigger value 0.1 % w/w (i.e. 1.5 % w/w) bear a potential (unacceptable) risk for human health for some uses (e.g. gloves used by industrial workers) according to the human risk assessment (section B.9.3). The selected limit for DMF in articles in this RMO allows most of the actors in the supply chain to to comply with this limit. Based on the comments received during the consultation process, the following consequences will be expected for the different industry sectors (more detailed information can be found in section F.4):

- Industrial gas industry: No significant impacts are to be expected, as European producers are currently using DMF under conditions that meet the standards corresponding to this RMO.
- Fiber industry: No significant impacts are to be expected, as European producers are currently using DMF under conditions that meet the standards corresponding to this RMO.
- Coating textile industry: Estimated impacts would be in the worst case **'Confidential information'** in identified monetary impacts. In the worst case **'Confidential information'** of the industry's turnover would relocate and **'Confidential information'** would use an alternative substance. In the best case, **'Confidential information'** of industry's turnover would be affected.
- Pharmaceuticals sector: This sector provided limited information regarding potential effects of analysed RMOs. Nevertheless, it shows that they would continue using DMF under RMO 4.
- Other industries: For some industries (agrochemicals, fine chemicals, phenolic resins, medical devices, sport industry, chemical industry and pigments-dyes), drawing general conclusions was not possible, as too few answers to the questionnaire were received. Overall, it only can be concluded that adopting RMO 4 rather than a complete restriction would allow avoiding negative socio-economic impacts in several different sectors.

E.2.5 Restriction option 5: Targeted Restriction

See section E.1.2 for an outline of the proposed restriction.

E.2.5.1 Effectiveness (risk reduction capacity and proportionality)

This RMO will fully reduce the risks of DMF for the uses addressed. Anyway, as long as a suitable (less harmful) alternative is not available, only alternatives with similar hazard profiles can be used to replace DMF. Further, no conditions are set to the uses that are not included in this targeted restriction and risks related to those uses as well as risks from articles containing DMF will remain. This option is not considered to be proportional, because the efforts needed from the actors to implement and from the authorities to enforce it, would be higher than the adverse effects that are being avoided, especially as not all identified risks can be addressed with this RMO.

E.2.5.2 Practicality (implementability, enforceability, manageability)

Even though necessary technologies, techniques and alternatives should be available, implementability and manageability is limited, as up to now the only alternatives available to replace DMF have similar hazards profiles.

The enforceability for the uses concered by this restriction should not cause any problems as for these it can be easily checked if DMF is still used or not.

E.2.5.3 Monitorability

Regarding monitorability, there are no specific concerns as this can be done through enforcement.

E.2.5.4 Overall assessment of Restriction Option 5

The risk reduction capacity of this RMO is limited: reduction of risk can only be ensured for the uses addressed, risks from articles containing DMF and risks related to those uses that are not included in this targeted restriction will remain. Regarding enforceability and monitorability there are no substantial differences to the other RMOs, but the practicability of this option is lower. As long as a suitable (less harmful) alternative is not available, only alternatives with similar hazard profiles can be used to replace DMF.

According to the comments received during the consultation process, the following consequences will be expected for the different industry sectors (more detailed information can be found in section F.4):

- Industrial gas industry: No significant impacts are to be expected, as European producers would not be affected by the targeted restriction corresponding to the RMO 5.
- Fiber industry: No significant impacts are to be expected, as European producers would not be affected by the targeted restriction corresponding to the RMO 5.
- Coating textile industry: Estimated impacts would be at least **'Confidential information'** in identified monetary impacts (in the worst case). In the worst case **'Confidential information'** of the industry's turnover would relocate and **'Confidential information'** would use an alternative substance. In the best case, **'Confidential information'** of industry's turnover would be affected.
- Other industries: For some industries (pharmaceuticals sector, agrochemicals, fine chemicals, phenolic resins, medical devices, sport industry, chemical industry and pigments-dyes), drawing general conclusions was not possible, as too few answers to the questionnaire were received.

E.2.6 Restriction option 6: Authorisation

In this section, the authorisation of DMF will be assessed, as DMF has already been included in the Candidate list for Annex XIV.

E.2.6.1 Effectiveness (risk reduction capacity and proportionality)

Risk reduction in case of an authorisation is expected to be comparable to restriction route, because in case authorisation is granted, exposure will be reduced to a value below the DNEL in those industries and no risks will remain. In the same way in case of restriction only the uses with exposure below the DNEL imposed would be allowed.

DMF exposure of consumers due to handling of DMF containing articles would remain the same. Since most of the articles with high concentrations of DMF residues are produced in Asia (please refer to section B.9.3) and imported into the EU, a certain risk for consumers will be still present – even after.

The compliance costs are expected to be comparable to RMO2-RMO3-RMO4, but the administrative costs (expecially the preparation of application for authorization, fee for application are expected to be much higher than other RMOs; wider socio-economic effects are expected to be comparable to RMO1.

Total economic effects of authorisation are expected to be larger than those of RMO2-3-4 but smaller than RMO1.

Requesting Authorisation is usually a great effort both for industry and for authorities. Economic disadvantages for EU users of DMF will emerge if comparable measures for safe DMF uses are not introduced outside of the EU. Due to a lack of alternatives, the outcome might be that the DMF using industry is leaving the EU. A restriction is considered more proportionate than Authorisation, as risk of use can be excluded by implementing restrictions for a defined set of "risky" uses and/or PROCs not unnecessarily harming clearly safe uses by inappropriate authorisation costs and phase-outs.

E.2.6.2 Practicality (implementability, enforceability, manageability)

The actors involved have to be capable in practice to comply with the Risk Management Measure. To achieve this, the necessary technology, techniques and alternatives should be available and economically feasible. For many applications, it is very difficult to substitute DMF and alternatives or

techniques for these uses are currently not known. Furthermore, many other available aprotic solvents have the same intrinsic properties with regards to reproductive toxicity as DMF (e.g. DMAC and NMP). From a risk management point of view polar aprotic solvents should be treated in a consistent way. The demand to substitute the substance due to its toxicological properties is already included in existing regulations and looking for alternatives to aprotic solvents of medium polarity has been rather unsuccessful, even after 20 years of research work. In general, it can be stated that industry supports substitution of DMF by other solvents, except the pharmaceutical industry. DMF plays a crucial role in the manufacturing and sterilisation of pharmaceuticals and in quality control applications. If DMF is totally restricted or an authorised use is not granted, these operations would be moved to non-EU countries and/or outsourced. For processes and applications that have been validated with DMF, it's much more practical to move the activities to outside the EU than to try to revalidate with solvents of unknown utility and with the uncertainty whether the new solvent may itself become authorized. Hence, as long as a suitable (less harmful) alternative is not available, the phase-out of DMF as aprotic solvent used by different industry sectors could not result in a benefit for human health. Due to the absence of suitable alternatives the authorisation route is clearly lacking implementability.

The compliance of relevant actors can be checked but will be specific for the different sectors as authorisation applications will be tailor-made. So far inspectorates do not have experiences in enforcing authorisation applications. This makes the enforceability more difficult.

Since risks are arising from DMF impurities in articles, the restriction route would need to be followed in addition, which will further increase the costs and adds a layer of complexity related to practicality and monitorability.The administrative requirements of authorisation and the uncertainties around these, are the main disadvantages of authorisation. Requesting for authorisation is costly and time-consuming, both for industry as for authorities especially given the widespread use of the substance. Besides, it gives large uncertainty to industry regarding the continuation of their business.

E.2.6.3 Monitorability

Regarding monitorability, there are no specific concerns as this can be done through enforcement.

E.2.6.4 Overall assessment of Restriction Option 6

The risk reduction capacity of this RMO is limited compared to the other RMOs, as the authorisation process cannot address risks arising from non-registered uses or risks to the consumer coming from DMF in imported articles. As requesting for authorisation is costly and time-consuming, instead a lot of companies will relocate their business to non-EU countries. In addition, increased imports from outside EU with no control on origin or quality might even increase health risks.

Approximately 85 % of the responding companies reported, that RMO 6 would force them to close at least parts of their business.

Regarding enforceability and monitorability there are no substantial differences, but the practicability of the authorisation route is lower compared to the other RMOs, as implementability is clearly lacking due to the absence of suitable alternatives.

According to the comments received during the consultation process, the following consequences will be expected for the different industry sectors (more detailed information can be found in section F.4):

- Industrial gas industry: Provided information was not sufficient for evaluation.
- Fiber industry: Provided information was limited in regard to evaluation. Nevertheless, it shows that authorisation would be as hard as a complete restriction.
- Coating textile industry: Estimated impacts would be at least **'Confidential information'** in identified monetary impacts (**'Confidential information'** in the worst case). **'Confidential information'** of the industry turnover would be affected by termination of production, **'Confidential information'** will opt for substitution and **'Confidential information'** would relocate its activities (best and worst case).

- Other industries: For some industries (pharmaceuticals sector, agrochemicals, fine chemicals, phenolic resins, medical devices, sport industry, chemical industry and pigments-dyes), drawing general conclusions was not possible, as too few answers to the questionnaire were received. In general, the pharmaceutical industry would take authorisation on a case by case basis, namely by applying for an Authorisation and, if granted, working towards substitution of DMF as required by the Authorisation. However, if a substitute was not found and a re-authorisation was not granted, then operations using DMF for this sector would be forced to move to non-EU countries and/or outsource the work to companies outside the EU.

E.3 Comparison of the risk management options

Table E.1 below provides an overview of the different RMOs compared against the key criteria effectiveness (risk reduction capacity & proportionality), practicality and monitorability. According to this, a partial restriction (RMO 2-4) would be the most appropriate risk management option and among the three possibilites the one with the highest concentration limit of DMF in articles (RMO 4) would be implemetable for the vast majority of actors in the supply chain without any big efforts or investements. RMO 4 is clearly related with the lowest socio-economic costs followed by RMO 3. RMO 2 ranks on the third position and RMO 1 on the fourth. Conversely, regarding risk reduction the lowest limit (RMO 2) of course would be the best solution.

To find the optimal risk management option that gives the best balance of the key criteria, the proposed restriction (see section E.5) is a refinement of RMO 2-4. The risk reduction potential of authorisation (RMO 6) is expected to be substantial and more or less equal to the risk reduction of restriction. However, there is a great uncertainty how industry will respond to authorisation. The costs (compliance costs and administrative costs) and wider socio-economic effects are expected to be very significant. Requesting for authorisation is costly and time-consuming, both for industry as for authorities. Moreover, there is a clear lack of alternatives. Therefore, RMO 6 is considered to be not proportional since existing risks can be managed by more appropriate risk management options.

Table E.1: Comparison of the identified RMOs against the key criteria.

Criterion	**RMO 1: Complete Restriction**	**RMO 2: Partial Restriction 1**	**RMO 3: Partial Restriction 2**	**RMO 4: Partial Restriction 3**	**RMO 5: Targeted Restriction**	**RMO 6: Authorisation**
Risk Reduction Capacity	+	++	++	+	+	+
Proportionality	--	++	++	++	-	--
Practicality (implementability, enforceability, manageability)	-	+	+	++	+	-
Monitorability	+	+	+	+	+	+

E.4 Main assumptions used and decisions made during analysis

For the main assumptions used and decisions made during the analysis see:

- Section B.9 (Exposure assessment), B.10 (Risk characterisation) and B.11 (Summary on hazard and risk)
- Section C for information on alternatives
- Section F for the qualitative and quantitative assessment of the health impacts and the SEA

E.5 The proposed restriction(s) and summary of the justifications

The analysis of the different identified RMOs – Total ban, partial restriction (with 3 different limits for DMF concentration in articles), targeted restriction and Authorisation – against the key criteria demonstrates that the restriction route should be the most appropriate Risk Management Option. In the case of a defined risk, as identified through the available exposure data, a restriction should be the preferable regulatory measure and consequently should be chosen as risk management option according to REACH. In contrast to a total ban, a targeted restriction or the Authorisation process, a partial restriction with the conditions as defined in E.1.2 would address all identified risks. Further, as it has been demonstrated that mostly risks are already adequately controlled and uses are safe, banning the manufacture and use of DMF in all or in some specific applications is not proportional.

According to E.3, a partial restriction (RMO 2-4) would be the most appropriate risk management option. Further refinement might be needed regarding the concentration limit of DMF in articles. A less conservative concentration limit for DMF in articles used by industrial workers than for DMF in consumer articles or even consumer articles for children is justifiable as risks to industrial workers will be further reduced by defined risk management measures (e.g. protective clothing and equipment).

In addition, the exposure control (inhalation) via a harmonized national OEL might not be optimal, as it is the only exposure limit that is outside the scope of REACH and the Scientific Committee on Occupational Exposure Limits (SCOEL) has its own method of deriving an OEL and has no legally binding or compelling reason to use the REACH methodology. Therefore, a harmonized DNEL for inhalative exposure is proposed instead (on the basis of the OEL as set out in the RMO 2-4). The advantage here would be that no further enforcement activities are required due to the implementation of such restriction.Concluding, the restriction proposed comprises the conditions as set out in table E.2 below.

Table E.2: Proposed restriction.

Designation of substance	Conditions of restriction
N,N-dimethylformamide EC No.: 200-679-5 CAS No.: 68-12-2	• Manufacturers, importers and downstream users of the substance on its own or in mixtures in a concentration equal or greater than 0.3% shall use in their chemical safety assessment and safety data sheets by [xx.yy.zzzz] a Derived No Effect Level (DNEL) value for workers inhalation of 15 mg/m^3 and a DNEL for workers dermal exposure of 0.79 mg/kg/day. • The professional use is permitted as laboratory reagent or solvent or for in-vitro diagnostics only. All other professional uses outside of laboratories are prohibited. • Articles used by industrial workers may not be placed on the market after [date] if they or parts thereof, contain DMF in concentrations higher than 1.5% by mass (w/w). The concentration limit should be applicable for each individual part of the article and should not be applicable for gloves. • Consumer articles and gloves for workers may not be placed on the market

	after [date] if they or parts thereof, contain DMF in concentrations higher than 0.1% by mass (w/w). The concentration limit should be applicable for each individual part of the article. • Consumer articles for children (e.g. toys, clothing, child care articles) may not be placed on the market after [date] if they or parts thereof, contain DMF in concentrations higher than 0.001% by mass (w/w). The concentration limit should be applicable for each individual part of the article.

F. Socio-economic assessment of the proposed restriction

This socio-economic analysis (SEA) considers the potential positive and negative impacts of the various risk management options defined in Chapter E. Part F.1 identifies human health risks resulting from the exposure to DMF and indicates how these risks would be reduced by the RMOs. F.3 sets the scene for the description of the socio-economic impacts of the RMOs that are evaluated in section F.4. In F.5 the uncertainties of the socio-economic analysis are described. F.6 constitutes a concluding section discussing the economic and technical feasibility of potential alternatives as well as the risk reduction capacity and the proportionality of the various RMOs.

F.1 Human health impacts

Based on the hazard characteristics of DMF and current estimated exposures for two specific process categories (PROCs), the risk characterisation leads to RCRs > 1 (see section B.9.1). A ban of particular applications (PROC 10, PROC 19) of DMF is assumed to result in a reduction in risks and consequently a reduction in negative health effects in humans.

In this section, impacts of the proposed restriction on human health will be discussed. The potential adverse human health effects of DMF are mainly based on results from animal studies. A qualitative description of these potential effects is given, followed by a description of attempts to quantify the effects. The effectiveness of the restriction is estimated in terms of the risk reduction capacity of the RMO, by assessing the decrease in risk (in terms of lowered RCRs) because of reduced exposure to DMF. A rough estimation is given of the size of the worker population exposed to DMF, for which a risk reduction is achieved by the various RMOs in this restriction proposal. The analysis is performed taking the EEA as a geographical scope. As such, potential changes in human health effects outside the EEA are not addressed.

F.1.1 Qualitative description of health effects of DMF

F.1.1.1 Developmental effects

As described in Part B of this restriction dossier, the most relevant affected human health endpoints of DMF are the reproductive and the developmental effects. It is concluded from the results of the continuous breeding study in mice that DMF exposure causes significant reproductive toxicity (e.g. reduced fertility and fecundity characterized by reduced pregnancy and mating index, reduced no. of litters and litter size) in the presence of general toxicity in females (increased liver weights, hepatocellular hypertrophy and decreased body weights). Moreover, reproductive toxicity of DMF resulted in affected prostate weight and epididymal spermatozoa concentration in the F1 parental males. Furthermore, it is concluded from several animal developmental studies performed via different exposure routes (dermal, oral and inhalation) that DMF exposure during gestation causes developmental toxicity, including embryo-/foetotoxicity and teratogenicity without overt maternal toxicity, pointing to a clear specific effect of DMF as developmental toxicant. Embryo- and fetotoxic effects were manifested by decreased number of liveborn pups, decreased number of litters, litters' size, and decreased foetal body weights. Teratogenic effects included external, skeletal and visceral malformations as well as increased incidence in variations and retardations was observed. In rats, embryo-/fetotoxicity and teratogenicity were mostly seen at maternal toxic doses, whereas in mice and in rabbits embryo- /fetotoxicity and teratogenicity occurred also at dose levels without maternal toxicity. However, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF.

Relevancy for humans

There is no information available in literature about cases of reproductive or developmental effects in humans after exposure to DMF. As described in the toxicokinetic summary (section B.5.1.3), ADME characteristics in animals and humans are similar. Furthermore, specific metabolite such as N-acetyl-S-(N-methylcarbamoyl) -cysteine (AMCC) is expected to be responsible for developmental toxic effects. Since this metabolite has also been identified in humans, the relevant reproduction and developmental effects demonstrated in rodents could also be relevant for humans. Furthermore, accumulations of AMCC in human body or rather high proportions of this metabolite in humans in comparison to rodents have been described. Based on this information, potential endpoint for further investigation in the human health impact assessment is:

- Increase in AMCC metabolite

F.1.1.2 Systemic health effects after chronic exposure

Chronic DMF exposure might result in negative health effects for all workers (female and male). In repeated-dose animal studies, the adverse systemic effects found were changes in body weight, changes in food consumption, hepatic injury and increased kidney weights. In an inhalation repeated dose toxicity study, minimal to mild hepatocellular hypertrophy was observed at all concentrations tested. In the oral exposure study, hepatic injury was further characterized by changes in clinical chemistry values, e.g. increased enzyme activities. Similarly with developmental effects, AMCC metabolite is assumed to be responsible for the occurrence of hepatotoxic effects.

At very high dose levels of DMF, exceeding MTD (section B.5.8), DMF produced neoplastic lesions in two rodent species. There were increased mortalities and increased incidences of benign and malignant neoplasms, hepatocellular adenomas and carcinomas and hepatoblastomas. These effects were seen only in two two-year inhalation studies, while no such effects were observed in the third two-year inhalation study in two rodent species or in any other long-term study. The incidences of testicular tumors in rats and mice were similar to control values.

In general, the most critical effect in the animal studies is based on hepatotoxicity.

Relevancy for humans

The extrapolation of the chronic systemic effects of DMF described in animals to humans could imply that a person would eat less and loose some body weight, probably combined with some loss in general well-being. The hepatotoxicity effects of DMF found in animal studies seem to be easily to extrapolate to human health effects. In this regard, different publications exist referring to medical surveillance data and human health effects associated with DMF exposure in different industry branches. The obtained results mainly refer to a chronic DMF exposure (workers exposed to DMF for several years). In one study among workers in an acrylic fibre factory, exposure to DMF vapour (< 30 mg/m³) for 5 years did not seem to entail a risk of liver cytolysis. Similar findings were indicated by two studies among workers exposed to DMF in a synthetic leather manufactory (0 – 5.13 ppm) and in a factory for the production of polyurethane (up to 7 ppm). However, DMF-induced liver damage was found in another study among synthetic leather workers exposed to high DMF concentrations (i.e. 25 – 60 ppm). High exposure concentrations were significantly associated with elevated alanine aminotransferase levels. Further symptoms such as epigastric pain, nausea and loss of appetite have occurred at DMF levels of 10 – 60 ppm. Besides hepatotoxicity, less tolerance to alcoholic beverages was determined in these cases. Reduced alcohol tolerance is one of the earliest manifestations of excessive exposure to DMF. The workers had flushing symptoms including abdominal pain, flushing of skin on face, and arms, reddening of eyes, stomach ache, nausea etc. Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Furthermore, ethanol induces cytochrome P450 2E1 which facilitates the initial hydroxylation of DMF. Thus, exposure to DMF can cause severe alcohol intolerance.

The effects of DMF found in other organs (kidney) in animal studies are difficult to extrapolate to human health effects. Whether specific effects to organs will occur in humans is uncertain. Besides, these effects are so-called sub-clinical and no clear disease can be determined for humans.

Regarding carcinogenic effects observed in two animal studies, there are predominantly hepatic, testicular and mammary gland tumors reported in animals while cases of testicular, prostate, oral cavity, throat, liver and skin cancers in workers of aircraft repair and leather tannery facilities exist. Moreover, the cases of these types of cancer failed to be confirmed in further studies. Additionally, confounders like smoking and coexposure to other chemicals have not always been taken into account.

Based on this information, potential endpoints for further investigation in the health impact assessment are:

- Decrease in body weight, body weight gain and food consumption
- General loss of well-being
- Hepatic injury (elevated enzyme levels)
- Potential effects on other organs
- Neoplastic lesions
- Alcohol intolerance.

F.1.2 Possibility of quantification of the health effects of DMF in humans

Text box 1: Possible methodology for a Health Impact Assessment for chemicals within REACH

According to Part 1 of the RPA (2011), the extent to which Risk Characterisation Ratios (RCRs) provide information with which to inform an SEA is limited, as they provide no information on the severity or extent of effects that might be anticipated to occur in an exposed population. Consecutively, the document lists different approaches how to appropriately quantify the change in health impacts:

• use of a simple physical indicator of change in risk as a proxy for impact; for example, change in usage, change in exposure levels and/or frequency, change in concentrations of a chemical in consumer products, or changes in emissions in the workplace or to the environment

• full quantification of the change in human health impact that may arise from the risk reduction measures under consideration.

Key elements in health impacts according to RPA report Chapter 6.1.1 are:

a) current levels of exposure to the chemical and the anticipated changes in exposure due to risk management

b) dose-response or other data linking exposure to different health outcomes

c) data on the population exposed both prior to and after regulation

d) based on the above, estimates of the number of cases of a particular disease outcome attributable to exposure to the chemical of concern (or chemicals more generally)

e) data on the economic value of changes in health outcomes.

Key elements a) to c) leading to d) can be quantified by using “health metrics” for which the RPA report (Chapter 6.1.2) provides 4 options (quoted):

1. “dose-response functions: these provide a direct indication of the probability that someone exposed to a substance at a given dose level will contract the health effect of concern. Epidemiological data are frequently inadequate to inform their development and they are not linked to the usually available epidemiological health metrics (odds ratio, relative risk ratio or attributable risk). They can, however, be derived from benchmark dose and margin of safety estimates using models which extrapolate from the underlying animal data;

2. attributable fractions: these provide an indication of the burden of disease within a population. Through the use of relative risk ratios or odds ratios, the impacts of changes in exposure – i.e. from current exposures to no exposure - on the attributable fraction can be calculated, indicating the associated reduction in the disease burden for the associated population;

3. prevalence or incidence: in the absence of a dose-response function or relative risk and odds ratios, statistical data on the prevalence or incidence of a disease within a population can be used to provide a starting point for predicting changes in impacts. However, this requires additional assumptions on how a change in exposure may change prevalence or incidence. For example, by calculating the difference in prevalence or incidence for an exposed and an unexposed population; and

4. the Risk Characterisation Ratio (RCR) together with the margin of safety (MOS): the margin of safety data on its own provides no means of quantifying the change in health impacts that would arise from a regulatory measure; it is only possible to quantify the change in impacts if the MOS data are fed into the various models that are available to allow extrapolation of a dose-response function."

Possible approaches to quantify health effect in humans are elaborated by RPA and summarized in textbox 1. The Dossier Submitter sees in theory two possible routes for quantitative health impact assessment (the points 1 and 3 as mentioned above). In the case of DMF, calculated exposure estimates, taken from the registration dossier(s), are available. For the endpoint of developmental toxicity, the clinical endpoint in the human situation can presumably be high percentages of AMCC metabolite which can serve as an indication of concern. Regarding endpoint chronic toxicity (hepatotoxicity), the clinical endpoints relevant for humans are cases of loss of well-being, elevated hepatic enzyme levels, alcohol intolerance as well as decreased body weight and food consumption. The fact, that some clinical endpoints (for example high proportions of AMCC in human body) or the related disease (cancer) in the human situation are not clear, provides difficulties for the quantification of human health effects. For DMF the Dossier Submitter sees little possibilities for quantification of the potential effects due to data constraints and high uncertainties. However, the possible routes will be further discussed to explain why specific quantification of health impacts in this case is not possible.

Both methods have been applied in previous restriction dossiers, as described in the textbox below.

Text box 2: Examples of HIA for chemicals

Approach A. Using dose-response relationship

(point 1 from the RPA report (2011))

In the restriction dossier on Lead in jewellry, a dose-response relationship established in humans between IQ levels and blood lead levels was used to assess the health impact (point 1). Using dose-response relationships, estimated number of the population exposed and making assumptions to extrapolate from animal studies to the human situation was also described in the report by Schuur et al. (2008). In nine cases involving restriction on chemicals in consumer products it was attempted to stretch the extrapolation, to find out what problems were encountered while going from risk assessment to health impact assessment. Health impact was assessed, however with large ranges surrounding the final numbers, expressed in Disability Adjusted Life Years (DALYs).

Approach B. Starting point is prevalence

(point 3 from the RPA report (2011))

The prevalence of skin allergy caused by Chromium was the starting point for the health impact assessment in the restriction dossier on Chromium VI in leather products (point 3). This approach could be used for the assessment of the health effects due to occupational exposure to chemicals uses the actual occurrence of a certain disease in the (worker) population as a starting point. From that point on one could try to estimate the contribution of exposure to a specific substance to the occurrence of the disease in the population. This approach was used e.g. by Baars et al. (2005), who performed an exploratory study on the burden of disease due to exposure to chemicals at the workplace. Nine diseases were linked to exposure to a substance, the number of cases per year were determined, and

combined with the assumed percentage of the disease due to occupational exposure to the substance. This was extended with another study with reproduction health effects as the endpoint (Dekkers et al., 2006). For this endpoint, experts on reproduction, on occupational exposure and on risk and health impact assessment, were brought together to perform an expert elicitation. With those results, the authors concluded on the impact (expressed in DALY's), but with a lot of discussion and a large uncertainty in the numbers.

Besides the approaches given in Textbox 2, an option to assess in some quantitative way the effectivity of the various RMOs in a restriction dossier on human health risks, is to assess the risk reduction capacity of the RMOs. An assumption can be made on the decrease in exposure caused by the implementation of a RMO. This will lead to a change, a decrease, in the RCRs. This approach (somewhat point 4 from the RPA report) is not a human health impact assessment, but merely a quantification of the effect of an RMO on RCRs. For DMF, it is described in F.1.3. as approach C.

F.1.2.1 Calculation based on experimental animal studies: from animal studies to human health impact (approach A)

A health impact assessment can be performed starting with animal study results, extrapolating from an adverse (subclinical) no-effect-level in an animal to an exposure level resulting in a disease in workers. For this assessment, the following steps need to be taken:

1. Determine the relevant health endpoints (adverse sub-clinical and clinical effects) in the target population based on effects observed in animals and (if available) humans.

2. Determine the effect level in animals (to be used as point of departure).

3. Translate effect levels in animals to effect levels in humans in order to define the exposure-effect relation in humans.

4. Extrapolate the adverse subclinical effect to a clinical effect in humans.

This exposure-effect relation could then be used to further quantify potential human health impacts by combining this with the expected decrease in exposure and the size of the population. To be able to make these extrapolations, a number of estimates or assumptions need to be made. The information to base such assumptions on is sufficient only in case of hepatotoxicity and alcohol intolerance. However, the above mentioned steps cannot be made at a sufficient level of certainty for the developmental and carcinogenicity endpoints, mainly due to the absence of relevant or reliable information about health impacts on humans. In the following tables, the different steps are described for developmental effects, and for systemic effects after chronic exposure (hepatotoxicity, carcinogenicity and alcohol intolerance).

Table F1. Theoretical steps for quantification of developmental effects of DMF

Extrapolation step	Explanation
1: Establishing relevant health effect in humans	Under F.1.1.1, a qualitative description is given of the possibility to extrapolate effects demonstrated in animals to effects in humans. Several metabolism studies in humans give an indication of potential effects in humans: high proportion of AMCC metabolite could be attributed to potential risk of developmental toxicity in humans. However, such sparse data (two obsolete studies) do not provide enough evidence to draw conclusions on.
2: No effect level to effect level in animal studies	In various developmental toxicity studies in rats, embryo-/fetotoxicity was mostly seen at maternal toxic doses/concentrations and teratogenicity was observed at maternal toxic doses/concentrations only, whereas in mice and in rabbits embryo-/fetotoxicity and/or indications for teratogenicity were found

	at dose levels without maternal toxicity.
3: Effect level in animal to effect level in human	In risk assessment, extrapolation factors are used to calculate from the NOAEL/C in animals to a safe level in human aiming to protect the human population for any adverse effects. In case of human health impact calculation, there is a need for a realistic extrapolation of exposure levels resulting in effects in animals (e.g. a LOAEL) to those in humans. For this approach, substance specific extrapolation factors would be required or assumptions need to be made introducing large uncertainties. As no human data is available on the exposure-effect relationship of the developmental endpoint and given the large uncertainties in quantitative extrapolation from animal effect levels to human effect levels, this step was considered not possible in case of DMF. An additional point of difficulty is the exposure (duration, timing) during gestation and the extrapolation to pregnancy.
4: Subclinical to clinical effects	High proportions of AMCC metabolite in humans exposed to DMF comparing to exposed animals are sub-clinical effects, suggesting another metabolic pathway of DMF in humans. The step from the observed sub-clinical effects to a specific disease in humans is, however, not possible.
5: Exposure decrease	To be able to assess the decrease in the exposure, an assumption should be derived on the effect of the different RMOs. With uncertainties, this could be done.
6: Size of the EU population exposed	Rough estimations are available for some use categories (see F.1.4).

Table F2. Theoretical steps for quantification of hepatotoxic effects of DMF

Extrapolation step	Explanation
1: Establishing relevant health effect in humans	Under F.1.1.2, a qualitative description is given of the possibility to extrapolate effects demonstrated in animals to effects in humans. Several human case studies give an indication of potential effects in humans: hepatic injury manifested by loss of well- being and elevated hepatic enzyme levels. Moreover, the potential human effects could also be reduced body weight (gain) and reduced food consumption. The case studies provide enough evidence to draw conclusions on.
2: No effect level to effect level in animal studies	In animals, hepatotoxic effects are observed at the LOAEL and higher dose levels at which adverse effects were observed, in contrast to the NOAEL at which no effects are observed.
3: Effect level in animal to effect level in human	The chronic exposure duration and timing in animals displays chronic exposure in humans. To extrapolate chronic NOAEL/C in animals to a safe level in human aiming to protect the human population for any adverse effects, extrapolation factors are used. In case of human health impact calculation, there is a need for a realistic extrapolation of exposure levels resulting in effects in animals (e.g. a LOAEL) to those in humans. For this approach, substance specific extrapolation factors would be required or assumptions need to be made introducing large uncertainties. As some human data are available on the exposure-effect relationship of the repeated dose toxicity endpoint and given no large uncertainties in quantitative extrapolation from animal effect levels to human effect levels, this step was considered to be reasonable in case of DMF.
4: Subclinical to clinical effects	Elevated hepatic enzyme levels, potentially reduced body weight and food consumption as well as loss of well-being are sub-clinical effects, so further extrapolation required here.

5: Exposure decrease	To be able to assess the decrease in the exposure, an assumption should be derived on the effect of the different RMOs. With uncertainties, this could be done.
6: Size of the EU population exposed	Rough estimations are available for some use categories (see F.1.4)

Table F3. Theoretical steps for quantification of chronic health effects (carcinogenicity) of DMF

Extrapolation step	Explanation
1: Establishing relevant health effect in humans	Under F.1.1.2. a qualitative explanation is given of the possibility to extrapolate effects seen in animals to effects in humans. Several human case studies give an indication of potential effects in humans: carcinogenicity manifested by the incidences of tumours of the testes, oral cavity, throat, liver and skin in workers. However, the case studies do not provide enough evidence to draw conclusions on because of confounding factors (like cigarettes consume and exposure to other solvents) as well as the fact that development of tumors could not be shown to be statistically significant or have correlation with the duration of exposure. Moreover, as for chronic effects, human (case) studies report various types of cancer but animal studies report predominantly increased incidence of hepatic cancer. Therefore, general adverse effects in animals could not be as one-to-one extrapolated to humans. For the more specific effects in organs (kidneys), no indications are given of potential effects in humans. Therefore, as no human studies are available, not enough evidence is available to draw conclusions on.
2: No effect level to effect level in animal studies	In the risk assessment, a NOAEL/C was derived for the described adverse health effects demonstrated in animal studies. From those studies, a LOAEC, the lowest level of exposure in the animal study where adverse effects were demonstrated, can be derived as well. Based on this information it is possible to indicate some kind of exposure- effect relationship in animals.
3: Effect level in animal to effect level in human	In risk assessment, extrapolation factors are used to calculate from the NOAEL/C in animals to a safe level in humans aiming to protect the human population for any adverse effects. In case of health impact calculation, there is a need for a realistic extrapolation of exposure levels resulting in effects in animals to those in humans. For this approach, substance specific extrapolation factors would be required or assumptions need to be made introducing large uncertainties. As some human data are available linking exposure levels to effects, a rough extrapolation, however with high uncertainties, may be possible in case of DMF.
4: Subclinical to clinical effects	Various types of cancer in humans and hepatic cancer in animals are clinical effects. However, types of cancers in humans and animals vary. That makes the step from adverse effects in animals to relevant, actual occurring clinical effects in the human situation rather difficult. The step from the observed clinical effects to a specific disease in humans is possible but associated with additional uncertainties.
5: Exposure decrease	To be able to assess the decrease in the exposure, an assumption should be made on the effect of the different RMOs. With uncertainties, this could be done.
6: Size of the EU population exposed	Rough estimations are available for some use categories (F.1.4).

Table F4. Theoretical steps for quantification of chronic health effects (alcohol intolerance) of DMF

Extrapolation step	Explanation
1: Establishing relevant health effect in humans	Under F.1.1.2. the effect of alcohol intolerance is reported only for humans. The effect is described in several human case studies: alcohol intolerance after exposure to DMF manifested by clinical symptoms which could be summarized as loss of well being. The case studies provide enough evidence to draw conclusions on. Alcohol intolerance is a specific effect of exposure to DMF and is an indication of hepatotoxicity in human beings. The effects have not been investigated in animals therefore an extrapolation does not apply in this case.
2: No effect level to effect level in animal studies	No animal studies exist for this effect; therefore an exposure-effect relationship in animals is not applicable.
3: Effect level in animal to effect level in human	Effect levels of alcohol intolerance in humans were identified. Therefore, an extrapolation from an effect level in animal to an effect level in humans does not apply.
4: Subclinical to clinical effects	Alcohol intolerance is a sub-clinical effect, therefore further extrapolation is required here.
5: Exposure decrease	To be able to assess the decrease in the exposure, an assumption should be made on the effect of the different RMOs. With uncertainties, this could be done.
6: Size of the EU population exposed	Rough estimations are available for some use categories (F.1.4).

F. 1.2.1.1. Quantification of chronic adverse health effects (carcinogenicity)

Various types of cancer are reported in workers exposed to DMF. However, there was no relationship with duration of exposure in several studies or the incidence cases were not linked to duration of exposure at all (no data about duration of exposure). Moreover, exposure levels were characterized as low (1 < 2 ppm), moderate (2 < 10 ppm) or high (>10 ppm). No significant increase in the incidence of tumors could be established for higher exposure levels. Therefore, no exposure-response correlation could be established based on these human data.. Taking into account very high exposure levels (exceeding MTD) in laboratory animals at which increased incidence of tumors was observed, and, probably, very high (> 10 ppm) exposure levels in humans, a rough semi-quantitative estimation can be made for carcinogenicity: tumors can occur in humans exposed to only very high dose levels to DMF during many years .

F. 1.2.1.2. Quantification of chronic adverse health effects (hepatotoxicity and alcohol intolerance)

In occupational exposure studies, hepatotoxicity and alcohol intolerance occurred in case of exposure to high concentrations of DMF. According to the publications included in the registration dossier there were no increases in serum hepatic enzymes in three populations of workers exposed to “moderate” (< 10 ppm) concentrations of DMF (Lauwerys et al., 1980; Yonemoto and Suzuki, 1980; Cai et al., 1992, Wrbitzky et al., 1999). However, according to the literature sources included in the OECD SIDS report (2004), increases in serum hepatic enzyme levels were reported for workers exposed to “high” (up to 60 ppm) concentrations of DMF. Health Canada (1999) distinguishes range of concentrations of DMF at which no increases in hepatic enzymes is being observed (1-6 ppm) from higher levels (> 7 ppm) at which the increases have been observed consistently (Health Canada, 1999). Based on this information, with regard to hepatotoxicity, the “low” concentrations of DMF (1-6 ppm) can be regarded as safe for humans. In the table below, exposure levels and occurrence of increases in serum hepatic enzyme levels

are presented.

Table F5. Overview of exposure-response information from cross-sectional human studies (adopted from Health Canada, 1999)

Exposure concentration	Increase in serum hepatic enzymes	Size of human population	Confounders	Reference
<10-60 ppm (area sampling)	Yes	183 workers	Some workers were also exposed to other solvents	Wang et al., 1999
10-42 ppm	Yes	13 workers	No data	Yang et al., 1994
5-20 ppm	Yes (significance not reported)	13 workers	Exposure to solvents	Tomasini et al., 1983
3-20 ppm (TWA, 7 ppm) personal sampling	Yes (significant increase)	100 workers	no	Cirla et al., 1984
7 ppm (area sampling at different workplaces	Yes (significant increase)	75 workers	no	Fiorito et al., 1997
0.2-8 ppm (area sampling)	Yes (significance not reported)	26 workers	Concomitant exposure to ACN*	Major et al., 1998
1-27 ppm	No	27 workers	no	Paoletti and Iannaccone, 1982
0.3-15.5 ppm (usually < 10 ppm; static area sampling)	No	22 workers	No	Lauwerys et al., 1980
0.1-7 ppm (personal sampling)	no	207 workers	Some workers were also exposed to toluene	Cai et al., 1992
1-5 ppm (personal and area sampling)	no	6 workers	No	Yonemoto and Suzuki, 1980
4-8 ppm (mean, 6 ppm; sampling not specified)	no	28 workers	No	Cattenacci et al., 1984
Up to 2.3 ppm (personal sampling)	no	126 workers	no	Wrbitzky and Angerer, 1998; Wrbitzky, 1999

*ACN: acrylonitrile

No associated symptoms have been reported in humans at “low” concentrations of DMF. Therefore, no loss of well-being can be expected either.

Since OEL value of 5 ppm has been taken as harmonized DNEL for long-term systemic toxicity effects by inhalation (see registration dossier), it should ensure that hepatotoxic effects will not occur in

humans (5 ppm corresponds to internal systemic dose of 2.1 mg/kg bw and is in the range of safe "low" concentrations of DMF, see Table F6). Therefore, if this DNEL is not exceeded and dermal exposure is minimized /or avoided, no further extrapolations for elevated enzyme levels to the manifested hepatotoxicity will be required. However, a health concern exists in case of simultaneous exposure via inhalation and via dermal routes. As worst case, internal body burden would amount up to 2.89 mg/kg bw DMF in this case (see also DNEL section). This internal dose results from 0.79 mg/kg bw (proposed harmonized dermal DNEL) and 2.1 mg/kg bw (resulting after inhalation exposure to 5 ppm (proposed harmonized inhalation DNEL) during 8-hour working shift). In such a hypothetical case when inhalation exposure can be excluded and only dermal exposure to DMF takes place, internal systemic dose would be 0.79 mg/kg bw (proposed harmonized dermal DNEL serves as worst-case). This dose is lower than 2.1 mg/kg bw resulting after inhalation exposure to 5 ppm. It means that dermal exposure only would not lead to exceeding of safe internal dose level for hepatotoxicity. Nevertheless, restriction for specific processes, which are associated with high exposure levels (i.e. PROC 10 and PROC 19 associated with high exposure via both inhalation and dermal routes), would result in the elimination of high risk applications and would lead to little number of cases of hepatic injury in workers.

Alcohol intolerance symptoms like nausea, vomiting, or flushing of the face and upper body have been associated with exposures to 10 ppm (30 mg/m³). As described above, in case of simultaneous exposure (dermal and inhalation), at least 2.89 mg/kg bw would be the internal dose while 30 mg/m³ would correspond to 4.28 mg/kg bw. It means that alcohol intolerance could occur by the conditions of considering OEL together with dermal contact to the substance. In some cases, workers responded to concentrations as low as 1.2 ppm (3.6 mg/m³) (Wrbitzky, 1999).

Summarizing, there are a lot of assumptions needed for the quantification of these health effects because of the variations in size of human populations investigated and magnitude and duration of exposure in different case studies as well as confounders (smoking and simultaneous exposure to other solvents). This will lead to a higher degree of uncertainty making the quantification not reliable. However, making rough estimation excluding or significantly minimizing number of activities with dermal exposure, the systemic internal dose can clearly be lowered to reach 2.1 mg/kg bw (resulting only from inhalation by considering OEL value of 5 ppm). The overview of the exposure levels is presented in the table below.

Table F6. Overview of exposure associated internal dose levels

	Exposure (ppm or mg/kg bw)	**Equivalent internal dose (mg/kg bw)***
No hepatotoxicity symptoms	1-6 ppm	0.43 - 2.5
Hepatotoxicity	>7 ppm	>3
Alcohol intolerance	>10 ppm	>4.28
OEL (systemic, inhalation)	5 ppm	2.1
Dermal DNEL	0.79	0.79 (based on dermal absorption of 100 %)
Cumulative dose in case of dermal and inhalation exposures (**without restriction**)		**2.89**
Cumulative dose after restriction (excluding PROC 10 and 19)		**is likely to be significantly lower than 2.89**

*calculated based on 10 m³ respiratory volume of workers during 8-hour working shift under light activity and body weight of 70 kg (example: 5 ppm is converted to mg/m³: mg/m³ = (MW x ppm)/ 24.5 where MW is molecular weight and 24.5 L is volume of ideal gas by 25 °C; 5 ppm corresponds to 14.9

mg/m³. This amount corresponds to 2.1 mg/kg bw: 149 mg inhaled by a person of 70 kg.)

Conclusion

For developmental effects, the first step of establishing the relevant human health effect or disease could be done, because there is some supporting information from human volunteer studies and cross-sectional case control studies. The relevant human health effect could be concluded to be increased levels of AMCC. However, quantitative steps to go from the NOAEL in animals to an effect level during pregnancy of a worker cannot be taken without making too many far-stretched assumptions.

For carcinogenicity effects, the relevant human health effects could be concluded by increased incidence of testicular and prostate cancer, cancer of the oral cavity and throat, liver and skin melanoma. However, no quantitative steps could be performed due to the fact that all cases of cancer in humans were not significantly different from controls and the exposure levels in humans are described as ranges (no exact concentration of DMF is known at which workers were exposed to). Moreover, taking into account the size of investigated human populations, magnitude and duration of exposure, extent of exposure to other substances, consideration of confounding factors like cigarette smoke and adequacy of reporting in these investigations, there is no consistent pattern of increase in incidence of various types of cancer in humans. Therefore, the available information from animal studies and few human data cannot serve as a basis to establish a dose-response function.

For chronic effects (hepatotoxicity and alcohol intolerance), the relevant human health effects are increased levels of hepatic enzymes and alcohol intolerance symptoms associated with decrease of well-being. Considering proposed harmonized inhalation DNEL of 5 ppm and harmonized dermal DNEL of 0.79 mg/kg bw eliminating critical processes (PROC 10, PROC 19) associated with a high risk for human health, internal systemic dose will be significantly lower than 2.89 mg/kg bw and therefore the incidence of cases of hepatic injury and/or alcohol intolerance symptoms will be lower.

Based on available information and accepted risk assessment methodologies, it can be determined whether or not subjects are at risk. The expectation is that DMF exposure can cause adverse effects in humans, however currently it is not possible to adequately quantify those adverse effects in the population.

F.1.2.2. Calculation based on prevalence and incidence studies on diseases caused by DMF (approach B)

This approach includes the use of incidence data, the number of people suffering from the disease, as a starting point. After that, assumptions have to be made about the percentage of the total number of people with the disease attributable to exposure to DMF.

Developmental effects

No incidence rates exist for developmental toxicity in humans related to DMF exposure. The incidence rates cannot be calculated either because no studies or human case reports exist for this endpoint. The elevated AMCC levels in humans is a sub-clinical effect which does not necessary lead to any form of developmental toxicity in humans and therefore could not serve as incidence case. No other disease can be singled out to be used as a starting point for such quantification.

Effects after chronic exposure (carcinogenicity effects)

In the table below, the incidence rates of tumor development in humans are presented.

Table F7. Incidence rates of tumors (all malignant neoplasms)*

Type of tumor	Exposure concentration	Incidence (% or SIR**)	Size of human population investigated	Confounders	Reference
Prostate cancer	High (> 10 ppm)	SIR: 4 observed cases vs. 2.4 expected	2530	Only DMF exposed cohort; affected persons: heavy smokers and heavy drinkers	Chen et al., 1999
Cases of cancer of the oral cavity and throat	High (> 10 ppm)	SIR: 6 observed cases vs. 1.6 expected			
Cases of cancer of the oral cavity and throat	Moderate (sometimes > 10 ppm)	SIR: 3 observed cases vs. 1.6 expected			
Malignant melanoma	High (> 10 ppm)	SIR: 5 observed cases vs. 5 expected			
Prostate cancer	4 plants with exposure levels: low (1 < 2 ppm); moderate (2 - <10 ppm); High (> 10 ppm)	0.49 %	8724	Only DMF exposed cohort	Walrath et al., 1989
Cases of cancer of the oral cavity and throat		0.45 %			
Liver cancer		0.07 %			
Testis		0.13 %			
Malignant melanoma		0.45 %			
Testicular germ cell cancer (seminoma and embryonal cell carcinoma)	No data	1.96 %	153	DMF only; solvent mixture containing 80 % DMF and 20 % unspecified	Ducatman et al., 1986
		0.59 %	680		
Embryonal cell carcinoma	No data	3 cases (no data on SIR)	No data	DMF, 2-ethoxyethanol, 2-ethoxyethanol acetate	Levin et al., 1987 Frumin et al., 1989
Screening study to identify testicular cancers	No data	0 %	51 of the 83 workers	No data (leather tannery)	Calvert et al., 1990

*All cases were not significantly different from controls (if compared with company and national rates).

**SIR - standardized incidence rates.

Effects after chronic exposure (hepatotoxicity and alcohol intolerance)

Incidence and prevalence rates exist for hepatotoxicity and alcohol intolerance symptoms after exposure to DMF. The literature data have been summarized in the following table.

Table F8. Incidence rates of elevated enzyme levels and alcohol intolerance cases*

Elevated enzyme/Alcohol intolerance symptoms	Exposure concentration	Incidence (% or SIR)	Size of human population investigated	Confounders	Reference
ALT ↑, AST ↑, GGTP ↑, AP↑	7 ppm (21 mg/m³)	16%	75	Excluded since liver hepatitis markers and alcohol consumption were stratified	Fiorito et al., 1997
Face flushing		38%			
Palpitation		30 %			
Headache, dizziness		22 %			
Body flushing		15 %			
Tremors		14 %			
Gastrointestinal symptoms (stomach pain, nausea, loss of appetite).		50 %			
Alcohol intolerance symptoms (all cases)	7.3 ppm (wet spinning); 6.4 ppm (dry spinning) 1.4 ppm (finishing; 2.5 ppm (dyeing)	71 %	126	Excluded	Wrbitzky and Angerer, 1998 Wrbitzky, 1999
Previous liver diseases, including increased liver function values	7.3 ppm (wet spinning); 6.4 ppm (dry spinning); 2.5 ppm (dyeing)	11 %			
	1.4 ppm (finishing)	5 %			
γ-GT ↑, AST ↑ and ALT ↑	1.4 ppm (finishing)	No data			
ALT ↑, AST ↑, GGTP ↑, AP↑	5- 20 ppm	15 %	13	Also other solvents	Tomasini et al., 1983

ALT- alanine aminotransferase; AST – aminotransferase; GGTP- g-glutamyl transpeptidase; AP - alkaline phosphatase

As seen in the table above, the incidences of increased enzyme levels occurred if exposure to DMF via inhalation is above 5 ppm (incidences of 16 %, 11, % and 15 % in case of exposure to 7, 2.5-7.3 and 5-20 ppm, respectively). In some cases, statistically significant increase in liver values was also noted in low (1.4 ppm) exposure group of workers (Wrbitzky, 1999). Moreover, DMF can cause liver diseases even if air OEL is respected, because accidental dermal contact with liquid DMF can significantly increase DMF uptake. As mentioned in the section F.1.2.1.2., in case of simultaneous exposure (dermal and inhalation), at least 2.89 mg/kg bw would be the internal dose while exposure to 15 mg/m³ (SCOEL value) would result in 2.14 mg/kg bw. It means that consideration of inhalation OEL value is no longer sufficient to protect workers against liver injury and alcohol intolerance symptoms. The incidence values presented in the table above resulted not only from inhalation exposure but a possibility of dermal exposure to DMF cannot be excluded, therefore the increased level of hepatic enzymes as well as symptoms of alcohol intolerance already cover simultaneous exposure to DMF. Excluding or minimizing exposure (due to the present restriction by means of excluding PROC 10 and 19), a significant decrease in the incidence of liver injury and/or alcohol intolerance would be expected. However, a reliable estimation of the proportion of cases attributable to exposure to DMF affected by this restriction is not scientifically possible due to the uncertainties in the calculation of "restriction" incidence rates. With other words, a lot of assumptions need to be made to establish reliable incidence rates in case PROC 10 and 19 will be excluded. Therefore, no proportion (comparison) between incidence rates before and after the restriction can be made.

Conclusion

For developmental effects, the first step of calculation the relevant human incidence case of a disease could not be performed, because there is no supporting information from human volunteer studies. The relevant human health effect could be concluded to be increased levels of AMCC. However, no cases of developmental toxicity exist for humans which were exposed to DMF and had high levels of AMCC.

For carcinogenicity effects, incidence rates exist for development of tumors in workers exposed to DMF. However, since standardized incidence rates (SIR) (observed versus expected from company rates) were not significant in several case-control studies on the one hand, and there was no relationship with duration and levels of exposure on the other hand, no estimation of the proportion of cases attributable to exposure to substances affected by this restriction dossier could be made.

For hepatotoxicity and alcohol intolerance, incidence rates exist in literature. However, an estimation of the proportion of cases attributable to exposure to DMF affected by this restriction is not scientifically possible due to the uncertainties in the calculation of incidence rates. Making a rough estimation, it is very likely, that excluding activities related to PROC 10 and 19, high exposure processes will be excluded and the percentages of incidence of hepatic injury and alcohol intolerance will be significantly lower.

F.1.3 Risk reduction capacity as indication of potential health effects (approach C)

The effects of the different RMOs on the human exposure levels can be assessed by comparison of the calculated Risk Characterisation Ratios (RCRs). A reduction of the acceptable DMF residue levels in articles will reduce exposure level towards workers and consumers; hence the respective RCR will also decrease. Therefore, the effectiveness of risk reduction capacity of the RMO on the human health risks can be assessed in terms of RCRs.

F.1.3.1 RMO 1: Total ban

RMO 1 is total ban for placing on the market and use of DMF for all applications. Such total ban will eliminate any industrial/professional exposure towards DMF at all. Therefore, the respective RCRs will decrease to zero (RCR = 0). It can be concluded that in case of RMO1, there will be no remaining risk for industrial/professional worker caused by DMF after implementation of the total ban.
A total ban is disproportionaly, because risky uses can be eliminated by restriction and safe uses could

be contained.

F.1.3.2 RMO 2 to 4: Reduction of acceptable DMF residue levels in articles

Different types of articles used by industrial/professional workers and consumers are known to contain DMF residues. In general, there is little information on concentration of DMF in articles and emissions from articles. However, due to widespread use of DMF in the plastic and related industry branches (e.g. artificial leather) outside EU, imported articles and consumer goods can contain relevant levels of DMF. Left part of following Table F9 summarises information regarding observed DMF residue concentration levels in articles based on publications. Regarding assessment for children, the estimated exposure values are compared with modified DNELs (decreased by a factor of 10) to account for this (more sensitive) subpopulation. Consecutively, exposure values are compared with a $DNEL_{inh}$ of 1.5 mg/m³, a $DNEL_{der}$ of 0.04 mg/kg bw/day and a $DNEL_{oral}$ of 0.04 mg/kg. For further details, refer to section B.9.3 of this document.

Furthermore, a risk assessment for relevant articles was performed and is described in Section B.9.3 of this dossier. The aim was to identify specific concentration levels in articles, which can be considered to be of acceptable risk for industrial/professional use and/or consumer applications.

For this purpose, different DMF concentrations (0.1, 0.3, and 1.5 % w/w) were used as input parameter for the modelling approach in order to define cut-off values under which an acceptable risk for the relevant population (worker/general public) is expected. Results of this risk evaluation are summarised in the right section of following TTable F9.

Table F9. Effectiveness of Partial Restrictions (RMO 2, RMO 3 and RMO 4) on the Risk Characterisation Ratios (RCRs) for workers (industrial and professionals) and consumers

Current situation								**Effect of Partial Restriction (RMO implementation)**					
			Worker-DNEL (inhal./dermal): 15 mg/m³ / 0.79 mg/kg bw/day **Consumer-DNEL* (inhal./dermal/oral): 15 mg/m³ / 0.4 / 0.4 mg/kg bw/day**					**Number of Risk Mitigation Option**					
								RMO 2 (max. 0.1 % w/w DMF)		**RMO 3 (max. 0.3 % w/w DMF)**		**RMO 4 (max. 1.5 % w/w DMF)**	
Use	**Article Category (AC)**	**Combined Exposure [mg/kg bw**	**RCR (oral)**	**RCR (inhala-tive)**	**RCR (dermal)**	**RCR (com-bined)**	**Conclusion of risk**	**Combined Exposure [mg/kg bw]**	**RCR combined**	**Combined Exposure [mg/kg bw]**	**RCR combined**	**Combined Exposure [mg/kg bw]**	**RCR combined**
RCRs Industrial uses													
Usage of gloves	AC 10	2.169	Not relevant	0.004	2.734	2.738	Up to 0.36 % w/w DMF was found (Zuther, 2011)	0.603	0.761	1.808	2.282	9.045	11.415
Handling of acrylic fibres	Not applicable (AC 0)	0.0183	Not relevant	0.0006	0.022	0.023	Up to 1.5 % w/w DMF was found (internal info textile industry)	0.001	0.002	0.004	0.005	0.0183	0.023
RCRs consumer uses													
Use of sport shoes / Adults	AC 5-1 AC 10-3	0.059	Not relevant	0.023	0.004	0.027	DMF conc. exceeds 0.005 % w/w in 60% of sampled shoes (Greenpeace, 2014)	1.185	0.548	3.552	1.639	17.768	8.220
Use of sport shoes / Toddlers	AC 5-1 AC 10-3	0.047	0.016	0.057	0.070	0.143		0.931	2.875	2.793	8.625	13.965	43.125
Use of	AC 10	2.008	0.063	0.546	1.548	2.157	Up to 0.36 % w/w	0.558	0.600	1.672	1.796	8.368	8.980

Current situation								Effect of Partial Restriction (RMO implementation)					
			Worker-DNEL (inhal./dermal): 15 mg/m³ / 0.79 mg/kg bw/day Consumer-DNEL* (inhal./dermal/oral): 15 mg/m³ / 0.4 / 0.4 mg/kg bw/day					Number of Risk Mitigation Option					
								RMO 2 (max. 0.1 % w/w DMF)		RMO 3 (max. 0.3 % w/w DMF)		RMO 4 (max. 1.5 % w/w DMF)	
Use	**Article Category (AC)**	**Combined Exposure [mg/kg bw**	**RCR (oral)**	**RCR (inhala-tive)**	**RCR (dermal)**	**RCR (com-bined)**	**Conclusion of risk**	**Combined Exposure [mg/kg bw]**	**RCR combined**	**Combined Exposure [mg/kg bw]**	**RCR combined**	**Combined Exposure [mg/kg bw]**	**RCR combined**
gloves / Adults							DMF was found (Zuther, 2011)						
Use of slimy toys / Toddlers	Not applicable (AC 0)	17.12	3.806	0.219	420.000	424.025	Up to 0.4 % m/m DMF was found (Danish MoE, 2005)	4.279	106.000	12.84	318.000	64.19	1590.000

*Further modification for children by 10-fold decrease of the standard Consumer DNEL (For details, please refer to section B.9.3.3.2.2 and et seqq.)

Remark:
Default values used for conversion of mg/m³ into mg/kg bw/day: Respiratory volume (10 m³ for workers, light activity; 5.8 m³ for toddlers, light activity); Body weight (70 kg for workers; 60 kg for consumers (adults); 10 kg for consumers (toddlers))

Articles which are used by industrial worker

Gloves:
Taking into account DMF residue levels up to 0.36 %, as observed by Zuther (2011), such **gloves** bear an unacceptable risk to industrial workers. The respective combined RCR amounts to 2.738, clearly exceeding the conservative trigger value of RCR ≤ 1 used for the article assessment (please refer to section B.9.3 for further information).

For comparison, a human risk assessment was performed based on DMF concentration levels of 0.1, 0.3 and 1.5 %, respectively. It was shown in the relevant contributing scenario that PU coated gloves containing 0.1 % DMF are of acceptable risk for industrial workers. These results were also assigned for professionals. Concentrations above this trigger value (i.e. 0.3 % w/w) bear a potential (unacceptable) risk for human health.

Acrylic fibres:
It was shown in a quantitative approach that acrylic fibres with a DMF concentration of ≤ 1.5 % w/w bear an acceptable risk for industrial workers if specific technical measures are implemented. **Articles which are used by consumers**

Use of sport shoes (adults and toddlers):
The observed DMF residue levels (> 0.005%; according to Greenpeace 2014) in sport shoes of adults are only of limited relevance, since no upper DMF value was reported. Taking the mentioned lower level of 0.005% DMF into account, wearing such sport shoes is assumed as not critical (RCR = 0.027 or 0.143 for adults and toddlers, respectively). Nevertheless, a reliable conclusion regarding potential risk level can not be drawn without data regarding the upper range of detected DMF values.

The performed exposure calculations for consumers show that a DMF concentration of 0.1 % w/w in football boots is of acceptable risk for adult consumers. An increased concentration of DMF residues leads to an unacceptable risk for human health. However, football boots which are used by children bear a potential risk for human health even at a DMF level of 0.1 % w/w (see table B98).

Use of gloves (adults):
As discussed above for gloves in the industrial sector, Zuther (2011) identified critical DMF residue levels. In compare with industrial applications, the contact periods and the total number of gloves used to be expected for consumer use are much lower. Nevertheless, a combined RCR of 2.157 was determined indicating a potential risk for consumers.

The outcome of the exposure assessment for gloves used by consumers can be summarised as follows: DMF residues in a concentration of 0.1 % w/w in gloves are considered to be of acceptable risk for consumers. The combined RCR is < 1. A concentration of 0.3 % w/w leads to a potential risk for human health. This assumption is based on the combined RCR which amounts to 1.796.

The results for the consumer use of gloves are similar to the results for the industrial use of gloves. However, for industrial use of DMF containing gloves the dermal exposure route is more critical (details given in section B.9.3.3.2.3 of this document). This is mainly based on the amount of gloves used daily. Contrary, for consumer use of gloves the inhalation exposure is more critical. Referring to exposure calculations for consumers, a relatively small room volume (20 m^3) is assumed for the modelling which explains this critical exposure route.

Use of slimy toys (toddlers):
The Danish Ministry of Environment found up to 0.4 % DMF in slimy toys (Danish MoE, 2005). Comparing this exposure with the manually defined DNELs for children (decreased by a factor of 10) leads to a combined RCR of around 424. Due to this result, an elevated risk towards children can be identified regarding use of slimy toys.

The chosen modelling approach definitely shows that DMF residues of 0.1 % w/w are not of acceptable risk for consumers (subpopulation: toddlers). Even at this low DMF level the revealed combined RCR amounts to around 106, indicating a strong risk for toddlers playing regularly with such slimy toys.

F.1.4 Population potentially at risk

The following table presents the number of employees exposed to DMF by industry. The information was collected through the questionnaire presented in Annex F1. Answers to the 7 were used to estimate the relevant numbers for industrial gases, fibers and textiles. The indicated numbers were extrapolated to the entire sectors using the extrapolation factors presented in Annex F1.

Table F10. Estimated number of employees exposed to DMF per year in the baseline scenario

Sector	Total number of employees[1]	Number of employees exposed to DMF	%
Industrial gases	[]	[]	[]
Fibers	[]	[]	[]
Textiles	[]	[]	[]

The following table reports the number of workers exposed to DMF under different RMOs. Under RMO1, DMF will have to disappear completely of all the production processes, so no employee in the EEA will be exposed For RMO2-RMO4, the number of employees exposed to DMF may be estimated by using the results presented in section F.4. For the industrial gases sector, []

For fibers, []

For textiles, []

Table F11. Estimated number of employees exposed to DMF under different RMOs

Sector	RMO 1	RMO 2	RMO 3	RMO 4
Industrial gases	[]	[]	[]	[]
Fibers	[]	[]	[]	[]
Textiles	[]	[]	[]	[]

F.2 Environmental impacts

As the dossier is targeted on potential human health effects, potential environmental effects are not considered in this restriction dossier.

F.3 Setting the scene for socio-economic impacts

F.3.1 The aim of the SEA

The present SEA has three purposes. First, it assesses whether the proposed restriction is the most appropriate Community-wide action compared to other RMOs. In that respect, it compares a potential partial restriction with a full restriction and a situation in which DMF is subject to the REACH authorization process.

[1] Total number of employees was estimated using answers provided in questionnaires and extrapolation factors, presented in Annex F1.

Second, it refines the scope of the proposed restriction. In that respect, it considers three options of a partial restriction and one option of targeted restriction, detailed in table below.

Table F12. Considered refinements of the proposed restriction

Partial restriction 1	• DMF shall not be manufactured and used by professional or industrial workers, unless: - the 8-hour TWA exposure will remain below 15 mg/m^3 and the 15 min peak exposure (STEL) remains below 30 mg/m^3; - dermal exposure is avoided by preventative measures to comply with the DNELs for dermal exposure; - the professional use is restricted to professional laboratories only. • Articles may not be placed on the market if they or parts thereof, contain DMF in concentrations higher than **0.1%** by mass (w/w). The concentration limit should be applicable for each individual part of the article.
Partial restriction 2	• DMF shall not be manufactured and used by professional or industrial workers, unless: - the 8-hour TWA exposure will remain below 15 mg/m^3 and the 15 min peak exposure (STEL) remains below 30 mg/m^3; - dermal exposure is avoided by preventative measures to comply with the DNELs for dermal exposure; - the professional use is restricted to professional laboratories only. • Articles may not be placed on the market if they or parts thereof, contain DMF in concentrations higher than **0.3%** by mass (w/w). The concentration limit should be applicable for each individual part of the article.
Partial restriction 3	• DMF shall not be manufactured and used by professional or industrial workers, unless: - the 8-hour TWA exposure will remain below 15 mg/m^3 and the 15 min peak exposure (STEL) remains below 30 mg/m^3; - dermal exposure is avoided by preventative measures to comply with the DNELs for dermal exposure; - the professional use is restricted to professional laboratories only. • Articles may not be placed on the market if they or parts thereof, contain DMF in concentrations higher than **1.5%** by mass (w/w). The concentration limit should be applicable for each individual part of the article.
Targeted restriction	Targeted Restriction: for the uses/mixtures/articles for which alternatives appear to be readily available, the use of DMF is banned (e.g. paints; glue, paint stripper; spraying; hand mixing etc.)

Third, it evaluates net socio-economic impacts for different RMOs. A detailed approach is presented in the Annex F1. It makes a distinction between direct costs detailed in table below (Table F13) and wider socio-economic impacts indicated in Table F14. Direct impacts represent the costs that will be incurred by downstream users as a result of the restriction. Wider economic impacts concern impacts on employees (in terms of lost jobs), indirect users (in terms of lost profits) and DMF producers (in terms of lost profits).[2]

Table F13. Overview of direct costs

Industry response	Costs
Business termination	Lost profits of direct users in the EEA Additional fixed costs of direct users (related to closing business in the EEA)
Business relocation	Additional fixed costs of direct users (related to closing business in the EEA)
Substitution	Additional fixed costs of direct users (for example process adaptation costs) Additional variable costs of direct users (for example additional production costs, additional administrative costs and substances and reformulation costs)

[2] Effects of SMEs, innovation and competitiveness were not analysed as too little information was provided in answers to the questionnaire.

Table F14. Overview of wider socio-economic impacts

Impacts	Possible causes
Lost jobs in the EEA	- Business termination - Business relocation
Lost profits of DMF producers	- Business termination - Substitution
Lost profits of indirect users	- Business termination - Business relocation - Substitution

In the ideal scenario, the SEA quantifies socio-economic impacts for the entire society, as detailed in the following table. A separate evaluation is then made for manufacturers, importers, downstream users, distributors and consumers. Conducting such a detailed SEA appears however disproportionate for a restriction dossier. The present SEA hence focuses on the most relevant impacts, detailed in the following table.

Table F15. Overview of affected actors

	Potential impacts	Analysed by ChemAdvocacy (Yes/no)
Manufacturers	Lost profits from sales of DMF	Yes
Importers	Lost profits from sales of articles containing DMF Increased profits from sales of articles using DMF	No No
Direct users	Lost profits from sales of articles containing and/or using DMF in the EEA because of business termination and/or relocation Additional costs caused by the substitution	Yes Yes
Indirect users	Lost profits from sales of articles containing and/or using DMF Additional costs caused by the substitution or relocation	No Yes
Consumers	Higher prices of concerned articles Worse quality of concerned articles Lost jobs	No No Yes

As Table F15 shows, different actors are considered in the evaluation of socio-economic impacts. A direct reaction consisting of business termination, business relocation, substitution or continued use of DMF is first studied. Its consequences for direct users in terms of lost profits and/or increased costs are next evaluated. Potential impacts for other concerned actors are also assessed. In particular, lost profits of DMF producers, increased costs of indirect users and lost jobs are evaluated. Details about the methodology used to estimate different impacts are presented in Annex F1.

Most of impacts are directly expressed in monetary terms and hence do not require monetization. Lost jobs constitute the only impact requiring monetization. The present SEA monetizes lost jobs by first estimating the average personnel costs and next multiplying the obtained result by the estimated number of lost jobs. Details of this approach are explained in Annex F1.

Impacts are evaluated by comparing a given RMO to the baseline scenario. The latter describes the outcome that would take place if the use of DMF was not restricted in any way. It is forecasted using the information about the actual use of DMF. Details about baseline scenarios for specific sectors are presented in section F.4.

All the impacts are evaluated for two cases: the best case and the worst case. There are two distinguishing factors between the two cases. The first factor concerns the considered reaction. For example, if a potential substitution for the use of DMF is currently unknown but could be discovered in the future, the substitution is only considered in the best case. The second factor is related to parameters used in the evaluation. For example, if a questionnaire indicates that 30-100% of business will be terminated, 30% is taken into account for the best case and 100% for the worst case. More information about differences between the best case and the worst case may be found in sections concerning specific industries and Annex F1.

F.3.2 Scope of the SEA

Geographic scope
The focus of the socioeconomic assessment is on the European Economic Area (EEA). Consultation of firms and quantitative impact assessment are drawn on a European basis.

Time horizon
A period of 15 years was considered. Fixed costs were counted only once, while variable costs were counted once for each year. Lost revenues related to business termination or relocation were also evaluated for the entire period. A discount factor of 4% was used.

F.4 Socio-economic impacts

F.4.1 Industrial gases industry

Baseline scenario
[]

RMO 1 – Complete restriction

[]

The following table presents the net present value of the identified impacts, using the approach presented in the Annex F1. Effects for the worst case are highly underestimated as very conservative assumptions were made to deal with missing data for acetylene users.

Table F16. Socio-economic impacts of the application of full restriction to the industrial gases sector

	Impacts	Best case	Worst case
DIRECT IMPACTS	Business termination costs (in M€)	[]	[]
	Substitution costs (in M€)	[]	[]
	Profit loss of direct users (in M€)	[]	[]
WIDER IMPACTS	Profit loss of indirect users (in M€)	[]	[]
	Profit loss of DMF suppliers(in M€)	[]	[]
	Number of lost jobs	[]	[]
	Value of lost jobs (in M€)	[]	[]
TOTAL INDENTIFIED MONETARY IMPACTS		[]	[]

RMO 2 – Partial restriction 1
[]

RMO 3 – Partial restriction 2

[]

RMO 4 – Partial restriction 3

[]

RMO 5 – Targeted restriction

[]

RMO 6 – Authorization

[]

Summary of the different RMOs on the industrial gas industry

[]

Table F17. Summary of socio-economic impacts of the application of considered RMOs to the industrial gases sector

	RMO1	RMO2	RMO3	RMO4	RMO5	RMO6
DMF producers (in M€)	[]	[]	[]	[]	[]	[]
Direct users (in M€)	[]	[]	[]	[]	[]	[]
Indirect users (in M€)	[]	[]	[]	[]	[]	[]
Lost jobs (in M€)	[]	[]	[]	[]	[]	[]
Total (in M€)	[]	[]	[]	[]	[]	[]

F.4.2 Fiber industry

Baseline scenario of the DMF use

[]

RMO 1 – Complete restriction

[]

Table F18. Differences between the best case and the worst case

Differentiating factor	Best case	Worst case
[]	[]	[]
[]	[]	[]
[]	[]	[]
[]	[]	[]

[]

Estimated impacts are presented in the following table.

Table F19. Socio-economic impacts of the application of full restriction to the fiber sector

	Impacts	Best case	Worst case
DIRECT IMPACTS	Business termination/reallocation costs (in M€)	[]	[]
	Profit loss of direct users (in M€)	[]	[]
WIDER IMPACTS	Profit loss of indirect users (in M€)	[]	[]
	Profit loss of DMF suppliers(in M€)	[]	[]
	Number of lost jobs	[]	[]
	Value of lost jobs (in M€)	[]	[]
TOTAL INDENTIFIED MONETARY IMPACTS		[]	[]

RMO 2 – Partial restriction 1

[] The estimated impacts are hence the same.

Table F20. Socio-economic impacts of the application of partial restriction 1 to the fiber sector

	Impacts	Best case	Worst case
DIRECT IMPACTS	Business termination/reallocation costs (in M€)	[]	[]
	Profit loss of direct users (in M€)	[]	[]
WIDER IMPACTS	Profit loss of indirect users (in M€)	[]	[]
	Profit loss of DMF suppliers (in M€)	[]	[]
	Number of lost jobs	[]	[]
	Value of lost jobs (in M€)	[]	[]
TOTAL INDENTIFIED MONETARY IMPACTS		[]	[]

RMO 3 – Partial restriction 2

[] The resulting impacts are presented in the following table. Details of the estimation are presented in Annex F1.

Table F21. Socio-economic impacts of the application of partial restriction 2 to the fiber sector

	Impacts	Best case	Worst case
DIRECT IMPACTS	Business termination/relocation costs (in M€)	[]	[]
	Profit loss of direct users (in M€)	[]	[]
WIDER IMPACTS	Profit loss of indirect users (in M€)	[]	[]
	Profit loss of DMF suppliers (in M€)	[]	[]
	Number of lost jobs	[]	[]
	Value of lost jobs (in M€)	[]	[]
TOTAL INDENTIFIED MONETARY IMPACTS		[]	[]

RMO 4 – Partial restriction 3

[]

RMO 5 – Targeted restriction

[]

RMO 6 – Authorization

[]

Summary of the different RMOs' impacts on the fiber industry

The summary of identified impacts is provided in the table below. **[]**

Table F22. Summary of socio-economic impacts of the application of considered RMOs to the fiber industry

	RMO 1	RMO 2	RMO 3	RMO 4	RMO 5	RMO6
DMF producers (in M€)	[]	[]	[]	[]	[]	[]
Direct users (in M€)	[]	[]	[]	[]	[]	[]
Indirect users (in M€)	[]	[]	[]	[]	[]	[]
Lost jobs (in M€)	[]	[]	[]	[]	[]	[]
Total (in M€)	[]	[]	[]	[]	[]	[]

F.4.3 Coating textile industry

Baseline scenario of the DMF use

[]

Applied methodology

[]

RMO 1 – Complete restriction

[]

Estimated impacts of these reactions are presented in the following table, for two different cases. Details on the determination of these cases and the methodology of estimation are presented in the Annex.

Table F23. Estimated impacts of RMO 1 for the coating textile industry

	Impacts	Best case	Worst case
DIRECT IMPACTS	Business termination/relocation costs (in M€)	[]	[]
	Profit loss of direct users (in M€)	[]	[]
	Substitution costs	[]	[]
WIDER IMPACTS	Profit loss of indirect users (in M€)	[]	[]
	Profit loss of DMF suppliers(in M€)	[]	[]
	Number of lost jobs	[]	[]
	Value of lost jobs (in M€)	[]	[]
TOTAL INDENTIFIED MONETARY IMPACTS		[]	[]

[]

RMO 2 – Partial restriction 1

[]

Estimated impacts of these reactions are presented in the following table. Details are presented in the Annex.

Table F24. Estimated impacts of RMO 2 for the coating textile industry

	Impacts	Best case	Worst case
DIRECT IMPACTS	Business termination/relocation costs (in M€)	[]	[]
	Profit loss of direct users (in M€)	[]	[]
	Substitution costs	[]	[]
WIDER IMPACTS	Profit loss of indirect users (in M€)	[]	[]
	Profit loss of DMF suppliers(in M€)	[]	[]
	Number of lost jobs	[]	[]
	Value of lost jobs (in M€)	[]	[]
TOTAL INDENTIFIED MONETARY IMPACTS		[]	[]

RMO 3 – Partial restriction 2

[]

Estimated impacts of these reactions are presented in the following table, for the two different cases. Details are presented in the Annex.

Table F25. Estimated impacts of RMO 3 for the coating textile industry

	Impacts	Best case	Worst case
DIRECT IMPACTS	Business termination/relocation costs (in M€)	[]	[]
	Profit loss of direct users (in M€)	[]	[]
	Substitution costs	[]	[]
WIDER IMPACTS	Profit loss of indirect users (in M€)	[]	[]
	Profit loss of DMF suppliers(in M€)	[]	[]
	Number of lost jobs	[]	[]
	Value of lost jobs (in M€)	[]	[]
TOTAL INDENTIFIED MONETARY IMPACTS		[]	[]

RMO 4 – Partial restriction 3

[]

Estimated impacts of these reactions are presented in the following table, for the two cases. Details are presented in the Annex.

Table F26. Estimated impacts of RMO 4 for the coating textile industry

	Impacts	Best case	Worst case
DIRECT IMPACTS	Business termination/relocation costs (in M€)	[]	[]
	Profit loss of direct users (in M€)	[]	[]
	Substitution costs	[]	[]
WIDER IMPACTS	Profit loss of indirect users (in M€)	[]	[]
	Profit loss of DMF suppliers(in M€)	[]	[]
	Number of lost jobs	[]	[]
	Value of lost jobs (in M€)	[]	[]
TOTAL INDENTIFIED MONETARY IMPACTS		[]	[]

RMO 5 – Targeted restriction

[]

Estimated impacts of these reactions are detailed in the following table, for the two cases. Details are presented in the Annex.

Table F27. Estimated impacts of RMO 5 for the coating textile industry

	Impacts	Best case	Worst case
DIRECT IMPACTS	Business termination/relocation costs (in M€)	[]	[]
	Profit loss of direct users (in M€)	[]	[]
	Substitution costs	[]	[]
WIDER IMPACTS	Profit loss of indirect users (in M€)	[]	[]
	Profit loss of DMF suppliers(in M€)	[]	[]
	Number of lost jobs	[]	[]
	Value of lost jobs (in M€)	[]	[]
TOTAL INDENTIFIED MONETARY IMPACTS		[]	[]

RMO 6 – Authorization

[]

Estimated impacts of these reactions are presented in the following table, for the two cases. Details are presented in the Annex.

Table F28. Estimated impacts of RMO 6 for the coating textile industry

	Impacts	Best case	Worst case
DIRECT IMPACTS	Business termination/relocation costs (in M€)	[]	[]
	Profit loss of direct users (in M€)	[]	[]
	Substitution costs	[]	[]
WIDER IMPACTS	Profit loss of indirect users (in M€)	[]	[]
	Profit loss of DMF suppliers(in M€)	[]	[]
	Number of lost jobs	[]	[]
	Value of lost jobs (in M€)	[]	[]
TOTAL INDENTIFIED MONETARY IMPACTS		[]	[]

Summary of the different RMOs' impacts on the coating textile industry

The summary of identified impacts is provided in the table below. []

Table F29. Summary of socio-economic impacts of the application of considered RMOs to the coating textile industry

	RMO1	RMO2	RMO3	RMO4	RMO5	RMO6
Termination/relocation (**M€**)	[]	[]	[]	[]	[]	[]
DMF producers (**M€**)	[]	[]	[]	[]	[]	[]
Direct users (**M€**)	[]	[]	[]	[]	[]	[]
Indirect users (**M€**)	[]	[]	[]	[]	[]	[]
Lost jobs (**M€**)	[]	[]	[]	[]	[]	[]
Total (**M€**)	[]	[]	[]	[]	[]	[]

F.4.4 Pharmaceuticals sector

[]

F.4.5 Other industries

For some industries, drawing general conclusions was not possible, as too few answers to the questionnaire were received. This was the case for the agrochemicals, fine chemicals, phenolic resins, medical devices, sport industry, chemical industry and pigments-dyes. Information provided for those industries is summarized below.

[]

F.5 Uncertainties in the socio-economic analysis

Uncertainties in the human health impact assessment:

Human health impact assessment: as described in section F.1, no quantitative human health impact

assessment has been prepared for this dossier. This is justified by several reasons:

- available data was found insufficient to quantify the potential effects (absence of developmental toxicity effects due to DMF exposure in humans);
- available animal data showed effects only in case of exceeding MTD and available human data showed no significant differences between exposed group and controls (carcinogenicity);
- high uncertainties exist by calculation of incidence rates of hepatic injury and alcohol intolerance in case of eliminating critical processes (i.e. PROC 10, PROC 19) associated with a high risk for human health.

The main reason was that no quantitative relationship could be derived between human health effects and exposure. Quantitative impacts would be quite uncertain so that the calculated numbers would not have an actual meaning. Instead of going for quantitative impacts, an (extensive) qualitative description was given next to some alternative quantitative proxies of the potential health effects (risk reduction potential, population of workers for which the risk is reduced) to provide insight in the magnitude of the potential effects.

Risk reduction (uncertainty of RCRs):

The exposure component in the RCRs contains uncertainties. The exposure estimates used are obtained from the registration dossier. These estimations were additionally expanded by a risk assessment referring to articles. Conclusively, exposure estimates for all uses and relevant articles have been provided, which need to result in a RCR below 1 taking into account the derived DNELs. It is possible that those estimates obtained using an exposure modelling tool are higher than the actual exposure values, as illustrated by the available measurements for manufacturers (refer to section B.9.1.1.1 and B.9.2.1). On the one hand, it is difficult to assess if modelling input parameters used like “use duration” or “LEV” are stretched to a maximum level (resulting in a RCR < 1), while the actual situation is different. On the other hand, the effectiveness of RMMs might be interpreted with a higher level than they have in the real workplace situation, resulting in underestimates. Furthermore, exposure scenarios for downstream uses might be interpreted differently. The reliability of the calculated exposures associated with the usage of articles is also extensively discussed in section B.9.3.4.

Assumptions on the effectiveness of the different RMOs were made in section F.1.3. The estimated exposures and calculated RCR values seem to be logic.

Uncertainties in the assessment of socio-economic impacts

The assessment of socio-economic impacts may be subject to three types of uncertainty. First, the quantitative assessment is not made for all the potentially affected industries. Quantitative results are only presented for industrial gas sector, fiber sector and textile sector, as too few answers were received for the other potentially affected industries. When reading results, one hence should bear in mind that presented results concern only a part of affected actors.

Second, received answers from companies or associations representing a given industry were extrapolated to entire industries. This poses uncertainty, as the exact data for non-responding companies are not known. In order to account for this type of uncertainty the turnover of companies which provided answers to the questionnaire was compared to the total market size. As the following table illustrates, answering companies and associations correspond to the majority of the concerned turnover. Potential extrapolation of the results hence does not seem to pose too much problem.

Table F30. Comparison of the turnover covered by the questionnaire with the estimated market size

Industry	Total estimated market size (in M€)	Turnover covered by the questionnaire (in M€)	%
Industrial gases	[]	[]	[]
Fibers	[]	[]	[]
Textiles	[]	[]	[]

Third, the accuracy of collected data and the robustness of the adopted methodology introduce uncertainty. In particular, estimations of market growth rates, estimations of total market size, as well as not declared margins, turnovers and closing costs may be subject to uncertainty. Furthermore, there is uncertainty concerning the firms' reactions. In order to deal with this type of uncertainty, two cases including best case and the worst case were studied.

F.6 Summary of the socio-economic impacts

F.6.1 Reduction in health effects

A restriction on DMF will result in a reduction in systemic health risks in all workers. As explained in section F.1, there will be reduction in risks for hepatotoxicity and alcohol intolerance symptoms whereby no quantitative description of the reduced human health impacts due to the various RMOs is given. Instead, the expected health gains are expressed in terms of risk reduction capacity explaining the effect of the various RMOs in terms of RCR reduction due to the decrease in exposure. For alternatives, a qualitative evaluation of a potential increase in risks (and potential health effects) due to the use of substance alternatives is performed by reviewing the hazard characteristics of alternatives. Furthermore, a quantitative estimate of the population potentially working with DMF that might experience health gains due to the various restriction options is provided.

RMO1 (complete restriction) is expected to result in a complete risk reduction of DMF both for industrial and (minor) professional uses. However, this reduction might be partially offset by an increase in risks caused by possible alternatives of DMF. For the (mainly industrial) uses where no alternatives are available, the total ban might result in a shift of DMF-using production facilities to non-European countries (like Asia and US). For these uses a risk reduction within the EU will be achieved (which will presumably be offset by an increase in risks outside Europe). The overall risk reduction of a total ban for industrial and professional worker within Europe is considered substantial, as the uses for which risks are potentially offset by the use of hazardous alternatives is assumed to be limited.

Referring to articles which contain DMF residues, risk reduction for consumers will be only slightly influenced by a complete restriction. The major concern of DMF exposure towards consumers is based on Asian products, which contain much higher DMF concentrations than comparable articles produced in the EU (please refer to the article assessment in Part B.9.3). Thus, risk reduction for consumers is not expected.

RMO2 (harmonized IOEL values, DMF concentration in articles ≤ 0.1 % w/w) is expected to result in substantial risk reduction of DMF - especially for industrial workers performing critical processes (PROC 10, PROC 19) and consumers handling articles that contain DMF residues. In the industrial sector, specific processes associated with high DMF exposures were identified for the production of fine chemicals, pharmaceuticals and polymers. These sectors will have to put substantial effort in exposure reduction as a consequence of RMO2. Due to general uncertainties associated with exposure

modelling tools which can often lead to an overestimation of exposure, it is assumed that high DMF exposures for specific activities can be significantly reduced by additional technical and/or operational measures. This will result in exposure levels below 15 mg/m³ (8h-TWA) and 30 mg/m³ (STEL).

With regard to consumer protection, RMO2 will have tremendous effects on the DMF residues in articles (for European articles and Asian import ware) which will lead to a substantial risk reduction for the general public. However, articles such as sports shoes and so called slimy toys for children containing equal or less than 0.1 % DMF in mass (w/w) still bear a potential risk. Conclusively, risk reduction for consumers will only be substantial for adults.

RMO3 (harmonized IOEL values, DMF concentration in articles ≤ 0.3 % w/w) is expected to result in substantial risk reduction of DMF for industrial workers performing critical processes (PROC 10, PROC 19) as demonstrated for RMO2. As already mentioned in the paragraph above, specific industrial sectors (production of fine chemicals, pharmaceuticals and polymers) will have to put substantial effort in exposure reduction as a consequence of this RMO. The effort is equal to the one discussed for RMO2.

Referring to ensuring consumer protection, RMO3 will lead to no significant risk reductions for the general public. According to the article assessment (section B.9.3), articles used by the industry (i.e. gloves) and articles used by the general public (i.e. gloves, sports shoes, slimy toys) still bear a potential risk towards human health for DMF concentrations equal to or less than 0.3 % by mass (w/w). Only the industrial usage of acrylic fibres was assessed to be safe for workers with DMF residues equal to 0.3 % w/w which is based on occupational and technical measures. In general, a lower risk reduction potential than RMO2 is, thus, guaranteed for RMO3.

RMO4 (harmonized IOEL values, DMF concentration in articles ≤ 1.5 % w/w) is expected to result in substantial risk reduction of DMF for industrial workers performing critical processes (PROC 10, PROC 19) as demonstrated for RMO2 and RMO3. As already mentioned in the paragraphs above, specific industrial sectors (production of fine chemicals, pharmaceuticals and polymers) will have to put substantial effort in exposure reduction as a consequence of this RMO. The effort is equal to the ones discussed for RMO2 and RMO 3.

With regard to consumer safety, RMO4 will lead to no significant risk reductions for the general public as also described for RMO3. According to the article assessment (section B.9.3), articles used be the industry (i.e. gloves) and articles used by the general public (i.e. gloves, sports shoes, slimy toys) bear a high potential risk towards human health if they contain DMF residues equal to 1.5 % w/w. Only the usage of acrylic fibres as article used by the industry was assessed to be safe for workers with DMF residues of 1.5 % w/w (operational and technical measures in place). Thus, a similar risk reduction potential as RMO3 and a lower risk reduction potential than RMO2 is guaranteed for RMO4.

To conclude, RMO2 has the largest potential risk reduction capacity in Europe beside RMO1 (complete restriction).

F.6.2 Technical and economic feasibility of substitution

Fiber industry

[]

Industrial gases

[]

Textile

[]

Fine chemicals

[]

Agrochemicals
[]

Phenolic resins
[]

IV diagnostics
[]

F.6.3 Proportionality

The following table presents a summary of identified impacts of analysed RMOs in millions of euros. RMO 5 and RMO 6 have been omitted due to the data availability problems. RMO 4 is clearly related with the lowest socio-economic costs followed by RMO 3. RMO 2 ranks on the third position and RMO 1 on the fourth.

Table F31. Overview of estimated socio-economic impacts (in M€)

	RMO 1	RMO 2	RMO 3	RMO 4
Industrial gases	[]	[]	[]	[]
Fibers	[]	[]	[]	[]
Textiles	[]	[]	[]	[]
Total	[]	[]	[]	[]

A complete proportionality analysis requires weighting identified socio-economic impacts against identified health risks, summarized in the following table. The health risk assessment shows that industrial articles, which have high concentrations (1.5%), can be handled safely due to occupational measures. In contrary, consumer articles with concentrations of > 0.1% pose significant health risks for adults. Similarly, articles from children with concentration above 0.001 % pose significant health risks for children.

Table F32. Risk reductions of RMO 1 – RMO 4

	Risk reduction of RMO 1	Risk reduction of RMO 2	Risk reduction of RMO 3	Risk reduction of RMO 4
Articles used by industrial workers	Complete	Substantial	Substantial	Substantial
Consumer articles for adults	Slight	Substantial	None	None
Consumer articles for children	Slight	None	None	None

The following restriction seems to balance well the identified socio-economic impacts with health risks. The evaluation of socio-economic costs suggests imposing a threshold of 1.5% on all the articles with traces of DMF. The evaluation of health risks indicates that such a level is acceptable only for articles used by industrial workers. The acceptable level of health risks may be only obtained if a threshold of 0.1% is imposed for consumer articles destined for adults and a threshold of 0.001% – for consumer articles destined for children. Furthermore, in order to eliminate health risks introduced by non-laboratory professional uses, professional use is only permitted as laboratory reagent or solvent or for in-vitro diagnostics.

Table F33. Proposed Restriction

Column 1: Designation of Substance	**Column 2: Conditions of Restriction**
XX. N,N-dimethylformamide EC No.: 200-679-5 CAS No.: 68-12-2	• Manufacturers, importers and downstream users of the substance on its own or in mixtures in a concentration equal or greater than 0.3% shall use in their chemical safety assessment and safety data sheets by [xx.yy.zzzz] a Derived No Effect Level (DNEL) value for workers inhalation of 15 mg/m^3 and a DNEL for workers dermal exposure of 0.79 mg/kg/day. • The professional use is permitted as laboratory reagent or solvent or for in-vitro diagnostics only. All other professional uses outside of laboratories are prohibited. • Articles used by industrial workers may not be placed on the market after [date] if they or parts thereof, contain DMF in concentrations higher than 1.5% by mass (w/w). The concentration limit should be applicable for each individual part of the article and should not be applicable for gloves. • Consumer articles and gloves for workers may not be placed on the market after [date] if they or parts thereof, contain DMF in concentrations higher than 0.1% by mass (w/w). The concentration limit should be applicable for each individual part of the article. • Consumer articles for children (e.g. toys, clothing, child care articles) may not be placed on the market after [date] if they or parts thereof, contain DMF in concentrations higher than 0.001% by mass (w/w). The concentration limit should be applicable for each individual part of the article.

G. Stakeholder consultation

G.1 General

Quite some information is available on DMF related its markets and use patterns. Beside the REACH Registration Dossier (Taminco, 2014), the Annex XV Dossier on DMF (Swedish Chemicals Agency, 2011) and the ECHA DMF Background Document (2013), the OECD SIDS (2004) was used as important sources for information. Nevertheless, extensive stakeholder consultation took place during the SVHC indentification process and the preparation of the Risk Management Option Analysis (Italian Ministry of Health, 2014) as well as when compiling the Restriction Proposal.

The public consultation on the Annex XV Dossier for Identification of DMF as SVHC started on the 3rd September 2012 and ended on 18th October 2012. 196 comments plus supporting documents were submitted by NGOs, EU Member States, industry, downstream users and industry organisations within this procedure (ECHA, RCOM 2012). On the 24th of June 2013 ECHA (2013) published a document developed in the context of ECHA's 5th Recommendation for DMF's inclusion in Annex XIV (Authorisation List). The 90 days period to give input to the draft prioritisation by ECHA did end on the 23rd of September 2013. Close to 205 pages with comments plus attached documents on ECHA's Draft 5th Recommendation for DMF were compiled by ECHA in the Responses to Comments Document (RCOM, 2014).

ECHA informed all DMF-Registrants on 21st of January 2014 via REACH-IT, that Italy is preparing a proposal to restrict the placing on the market of DMF according to REACH Article 69. Moreover, direct contact was made with the Lead Registrant and member registrants and several downstream users covering the main applications of DMF. DMF manufacturers and downstream users organised themselves within a DMF Task Force in order to collect and provide information requested by Italy for the preparation of the restriction proposal. The Italian CA organised several calls or meetings (e.g. 16th October 2013, 6th March 2014, May 5th 2014, and July 3rd 2014) together with the DMF Task Force. Many phone calls and email contacts were made during the proposal preparation phase in order to clarify questions.

Questionnaire on Exposure:
The Lead Registrant has provided the results of a Tier 2 Exposure Assessment (conducted in 2013) which was based on Exposure & Release Questionnaires, involving the Leads industrial customers using DMF as downstream users and as well all EU manufacturers. Through these questionnaires, all relevant exposure related information associated with human health and the environment was requested by referring to the REACH Use descriptor system. Each downstream user provided one questionnaire for any relevant Exposure Scenario. On the one hand, general data such as total tonnages, releases to the environment (including waste management) and descriptors for Sector of Uses (SU) and Product Categories (PC) were gained. Moreover, very specific process related information was received. This included the characterisation of performed applications, their Operational Conditions (OCs) and applied Risk Management Measures (RMMs). In addition, measured data for different DMF related activities were requested. Overall, more than 50 companies from different industry sectors provided more than 75 questionnaires. Due to this extensive feedback, the identification and assessment of relevant Identified Uses (IUs) was quite reliable. The objective of this data gathering exercise was to update and refine the Chemical Safety Assessment and Chemical Safety Report (CSA and CSR) and to identify critical process categories (PROCs) related to "Industrial Use", where additional RMMs might be necessary. The results are displayed in Section B and have been obtained from the Lead Registrant Taminco BVBA through a trustee (Chemservice S.A.), who prepared the questionnaires and compiled and anonymized all obtained information. The Questionnaires are attached in the Appendix of Section G as Annex G1 and G2.

Questionnaire on SEA:
A questionnaire for the Socio-Economic Analysis (SEA) was sent out on the 28th of June to the DMF Task Force. This Questionnaire is included in the Appendix as Annex F2 and was used to collect information on the use, revenues, costs, socio and economic impacts and alternatives. The impact on different risk management options (RMOs) were requested as well. More than 40 questionnaires and consolidated data from different industry sectors were received.

Questionnaire on Articles for Member States:
In July 2014 the Italian CA sent out a questionnaire (Annex G3) in order to collect information from other Member States related to existing restriction of DMF in articles as well as to collect information concerning exposure of consumers to DMF in consumer articles. The response was pretty scarce. In September 2014 a draft version of the (non-confidential) Restriction Proposal has been sent to the industry stakeholders (DMF Task Force). Received comments and recommendations have been taken into account when finalising the dossier. Information obtained via stakeholder communication might be referenced as "personal communication". Companies and industry organisations, which were involved in the Italian consultation, are as follows:

- ALCANTARA
- Alkylamines REACH Consortium
- Assogas Tecnici
- Assosistema
- BASF
- Centro REACH
- CEPSA
- CIRFS
- COIM
- CONFINDUSTRIA PRATO
- CRESPI
- DMF Task Force
- DOW
- ECPA
- ENDURA
- EFPIA Pharma ChemLeg
- EIGA
- EURATEX
- Federatione Gomma Plastici
- Federchimica
- HELM
- IVC
- Lyondell Basell
- Noreco
- Novotex
- PRAXAIR
- Repsol
- Sabic
- SAPIOR
- Shell
- SIFAVITOR
- SOL
- Solvay
- Syngenta
- Taminco
- TEVA

G.2 Industry response to different risk management options

The information was gathered through the questionnaire related to the Socio-Economic Analysis, which presented six different Risk Management Options (RMOs). Detailed results related to the SEA questionnaire are available in Section F. The different RMOs are explained in detail in Section E and in a nutshell in Section A. The following conclusions can be drawn for the industry stakeholders.

'Confidential information' of the companies who responded indicated that RMO 1 would force them to close at least parts of their business.

Around '**Confidential information'** of the responding companies stated, that RMO 2 would force them to close at least parts of their business.

Nearly **'Confidential information'** of the responding companies communicated, that RMO 3 would force them to close at least parts of their business.

About **'Confidential information'** of the responding companies declared, that RMO 4 would force them to close at least parts of their business.

'Confidential information' of the responding companies stated, that RMO 5 would force them to close at least parts of their business.

Approximately **'Confidential information'** of the responding companies reported, that RMO 6 would force them to close at least parts of their business.

H. Other Information

No additional information has been included because it was not considered necessary.

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APPENDICES

Appendices Section B

Annex B1: Complete exposure assessment and risk characterisation

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9. EXPOSURE ASSESSMENT (and related risk characterisation)

9.0. Introduction

9.0.1. Overview of uses and Exposure Scenarios

Tonnage information:

Assessed tonnage: **'Confidential information'** tonnes/year based on:

- **'Confidential information'** tonnes/year manufactured

The following table list all the exposure scenarios (ES) assessed in this CSR.

Table 100. Overview of exposure scenarios and contributing scenarios

Identifiers	Market Sector	Titles of exposure scenarios and the related contributing scenarios	Tonnage (tonnes per year)
ES1 - M1		Manufacture - Manufacture of substance - Manufacture of substance (ERC 1) - Use in closed process, no likelihood of exposure [Condition 1] (PROC 1) - Use in closed process, no likelihood of exposure [Condition 2] (PROC 1) - Use in closed, continuous process with occasional controlled exposure [Condition 1] (PROC 2) - Use in closed, continuous process with occasional controlled exposure [Condition 2] (PROC 2) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 1] (PROC 8b) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 2] (PROC 8b) - Use as laboratory reagent (PROC 15)	**Confidential information**
ES2 - F1		Formulation - Formulation of substance - Formulation in materials (ERC 2) - Use in closed process, no likelihood of exposure (PROC 1) - Use in closed, continuous process with occasional controlled exposure (PROC 2)	**Confidential information**

Identifiers	Market Sector	Titles of exposure scenarios and the related contributing scenarios	Tonnage (tonnes per year)
		- Use in closed batch process (synthesis or formulation) (PROC 3) - Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4) - Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) (PROC 5) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities (PROC 8a) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b) - Transfer of substance or preparation into small containers (dedicated filling line, including weighing) (PROC 9) - Use as laboratory reagent (PROC 15)	
ES3 - IW1		Use at industrial site - Industrial use for the production of fine chemicals - Industrial use of processing aids in processes and products, not becoming part of articles (ERC 4) - Industrial use resulting in manufacture of another substance (use of intermediates) (ERC 6a) - Industrial use of reactive processing aids (ERC 6b) - Industrial use of sub-stances in closed systems (ERC 7) - Use in closed process, no likelihood of exposure [Condition 1] (PROC 1) - Use in closed process, no likelihood of exposure [Condition 2] (PROC 1) - Use in closed, continuous process with occasional controlled exposure [Condition 1] (PROC 2) - Use in closed, continuous process with occasional controlled exposure [Condition 2] (PROC 2) - Use in closed batch process (synthesis or formulation) [Condition 1] (PROC 3) - Use in closed batch process (synthesis or formulation) [Condition 2] (PROC 3) - Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 1] (PROC 4) - Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 2] (PROC 4) - Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 3] (PROC 4) - Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) (PROC 5) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 1] (PROC 8a) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities	**Confidential information**

Identifiers	Market Sector	Titles of exposure scenarios and the related contributing scenarios	Tonnage (tonnes per year)
		[Condition 2] (PROC 8a) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 1] (PROC 8b) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 2] (PROC 8b) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 3] (PROC 8b) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 4] (PROC 8b) - Transfer of substance or preparation into small containers (dedicated filling line, including weighing) (PROC 9) - Production of preparations or articles by tabletting, compression, extrusion, pelletisation (PROC 14) - Use as laboratory reagent [Condition 1] (PROC 15) - Use as laboratory reagent [Condition 2] (PROC 15) - *Hand-mixing with intimate contact and only PPE available (PROC 19)**	
ES4 – IW2		Use at industrial site – Industrial use for the production of pharmaceuticals - Industrial use of processing aids in processes and products, not becoming part of articles (ERC 4) - Industrial use resulting in manufacture of another substance (use of intermediates) (ERC 6a) - Industrial use of reactive processing aids (ERC 6b) - Industrial use of sub-stances in closed systems (ERC 7) - Use in closed process, no likelihood of exposure [Condition 1] (PROC 1) - Use in closed process, no likelihood of exposure [Condition 2] (PROC 1) - Use in closed, continuous process with occasional controlled exposure (PROC 2) - Use in closed batch process (synthesis or formulation) [Condition 1] (PROC 3) - Use in closed batch process (synthesis or formulation) [Condition 2] (PROC 3) - Use in closed batch process (synthesis or formulation) [Condition 3] (PROC 3) - Use in closed batch process (synthesis or formulation) [Condition 4] (PROC 3) - Use in closed batch process (synthesis or formulation) [Condition 5] (PROC 3) - Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4) - Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) (PROC 5)	**Confidential information**

Identifiers	Market Sector	Titles of exposure scenarios and the related contributing scenarios	Tonnage (tonnes per year)
		- Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 1] (PROC 8a) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 2] (PROC 8a) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 1] (PROC 8b) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 2] (PROC 8b) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 3] (PROC 8b) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 4] (PROC 8b) - Transfer of substance or preparation into small containers (dedicated filling line, including weighing) (PROC 9) - Use as laboratory reagent (PROC 15) *- Hand-mixing with intimate contact and only PPE available (PROC 19)**	
ES5 - IW3		Use at industrial site - Industrial use for the production of polymers - Industrial use of processing aids in processes and products, not becoming part of articles (ERC 4) - Industrial use resulting in manufacture of another substance (use of intermediates) (ERC 6a) - Industrial use of monomers for manufacture of thermoplastics (ERC 6c) - Industrial use of process regulators for polymerisation processes in production of resins, rubbers, polymers (ERC 6d) - Industrial use of sub-stances in closed systems (ERC 7) - Use in closed process, no likelihood of exposure [Condition 1] (PROC 1) - Use in closed process, no likelihood of exposure [Condition 2] (PROC 1) - Use in closed, continuous process with occasional controlled exposure [Condition 1] (PROC 2) - Use in closed, continuous process with occasional controlled exposure [Condition 2] (PROC 2) - Use in closed, continuous process with occasional controlled exposure [Condition 3] (PROC 2) - Use in closed batch process (synthesis or formulation) [Condition 1] (PROC 3) - Use in closed batch process (synthesis or formulation) [Condition 2] (PROC 3) - Use in closed batch process (synthesis or formulation)	**Confidential information**

Identifiers	Market Sector	Titles of exposure scenarios and the related contributing scenarios	Tonnage (tonnes per year)
		[Condition 3] (PROC 3) - Use in closed batch process (synthesis or formulation) [Condition 4] (PROC 3) - Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 1] (PROC 4) - Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 2] (PROC 4) - Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 3] (PROC 4) - Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 4] (PROC 4) - Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 5] (PROC 4) - Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 6] (PROC 4) - Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) (PROC 5) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 1] (PROC 8a) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 2] (PROC 8a) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b) - Transfer of substance or preparation into small containers (dedicated filling line, including weighing) (PROC 9) - *Roller application or brushing (PROC 10)** - Use as laboratory reagent (PROC 15)	
ES6 - IW4		Use at industrial site - Industrial use for the production of textiles, leather and fur - Industrial use of processing aids in processes and products, not becoming part of articles (ERC 4) - Industrial use resulting in manufacture of another substance (use of intermediates) (ERC 6a) - Industrial use of monomers for manufacture of thermoplastics (ERC 6c) - Industrial use of process regulators for polymerisation processes in production of resins, rubbers, polymers (ERC 6d) - Use in closed process, no likelihood of exposure (PROC 1) - Use in closed, continuous process with occasional controlled exposure (PROC 2) - Use in closed batch process (synthesis or formulation) (PROC 3) - Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4) - Mixing or blending in batch processes for formulation of	**Confidential information**

Identifiers	Market Sector	Titles of exposure scenarios and the related contributing scenarios	Tonnage (tonnes per year)
		preparations and articles (multistage and/or significant contact) (PROC 5) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b) - Transfer of substance or preparation into small containers (dedicated filling line, including weighing) (PROC 9)	
ES7 - IW5		Use at industrial site - Industrial use for the manufacture of non-metallic mineral products - Industrial use of processing aids in processes and products, not becoming part of articles (ERC 4) - Use in closed process, no likelihood of exposure (PROC 1) - Use in closed, continuous process with occasional controlled exposure (PROC 2) - Use in closed batch process (synthesis or formulation) (PROC 3) - Industrial spraying (PROC 7)	**Confidential information**
ES8 - IW6		Use at industrial site - Industrial use for the manufacture of perfumes / fragrances - Industrial use of substances in closed systems (ERC 7) - Use in closed batch process (synthesis or formulation) (PROC 3) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b)	**Confidential information**
ES9 - PW1		Use by professional worker - Professional use as laboratory agent - Professional use as laboratory agent (ERC 8a) - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities (PROC 8a) - Use as laboratory reagent (PROC 15)	**Confidential information**
Manufacture: M-#, Formulation: F-#, Industrial end use at site: IW-#, Professional end use: PW-#, Consumer end use: C-#, Service life (by workers in industrial site): SL-IW-#, Service life (by professional workers): SL-PW-#, Service life (by consumers): SL-C-#.)			

* PROC 10 and PROC 19 are applications which are included in the uses advised against. In conclusion, these use descriptors are neither included in section 3.5 of the IUCLID file nor displayed in section 2.1 and 2.2 of this CSR. With regard to chapter 9 of this CSR, exposure modelling by CHESAR v2.2 was performed for PROC 10 and PROC 19 to identify/confirm a potential risk for human health associated with these processes.

9.0.2. Introduction to the assessment

The substance Dimethylformamide (CAS 68-12-2) is used as aprotic polar solvent in several industry sectors. It is mainly used for the production of fine chemicals (i.e. pharmaceuticals) and polymers. Another important use of this substance is for the production of textiles, leather and fur. With regard to the assumed tonnages, the industrial use for the manufacture on non-metallic mineral products and the manufacture of perfumes and/or fragrances are less important uses. The only professional use is

described by the use as laboratory agent.

In order to perform an adequate update of the risk assessment, all Downstream Users of the Lead Registrant were requested to provide specific information regarding their use patterns of the substance. For this purpose, two consecutive questionnaires were provided to the Downstream Users. In accordance with the REACH Use Descriptor System, information regarding the relevant Sector of Use (SU), Product Category (PC), Article Category (AC), Process Category (PROC) and Environmental Release Category (ERC) were gained in the first questionnaire. In addition, other important assessment parameters such as tonnages, measured data, Operational Conditions (OCs) and Risk Management Measures (RMMs) for each application/process were requested via a second questionnaire. After receiving all relevant information, the Identified Uses of the substance were revised accordingly.

The risk assessment for the substance was performed using CHESAR v2.2 to assess human exposure and to predict environmental concentrations. With regard to the human health assessment, exposure calculations using CHESAR were performed as TIER 1 approach. Due to the fact that relevant measured data from several different industrial sites is available, a TIER 2 assessment was additionally elaborated (refer to Section 9a of this document).

9.0.2.1. Environment

Scope and type of assessment

The scope of exposure assessment and type of risk characterisation required for the environment are described in the following table based on the hazard conclusions presented in section 7.

Table 101. Type of risk characterisation required for the environment

Protection target	Type of risk characterisation	Hazard conclusion (see section 7)
Freshwater	Quantitative	PNEC aqua (freshwater) = 30 mg/L
Sediment (freshwater)	Quantitative	PNEC sediment (freshwater) = 115.2 mg/kg sediment dw
Marine water	Quantitative	PNEC aqua (marine water) = 3 mg/L
Sediment (marine water)	Quantitative	PNEC sediment (marine water) = 11.52 mg/kg sediment dw
Sewage treatment plant	Quantitative	PNEC STP = 123 mg/L
Air	Not needed	No hazard identified
Agricultural soil	Quantitative	PNEC soil = 56.97 mg/kg soil dw
Predator	Not needed	No potential for bioaccumulation

Comments on assessment approach:

The regional concentrations are reported in section 10.2.1.2 (see Table 125, “Predicted regional exposure concentrations (Regional PEC)”). The local Predicted Exposure Concentrations (PECs) reported for each contributing scenario correspond to the sum of the local concentrations (C_{local}) and the regional concentrations (PEC regional).

Caution: The exposure estimates have been obtained with EUSES although the following parameter(s) is/are outside the boundaries of the EUSES model:

- Degradation Rate Constant with OH radicals (2E-9 cm^3 molecule-1 s-1)
- Half-life in air (2 h)

- Water solubility (1E3 g/L)

9.0.2.2. Man via environment

Scope and type of assessment

The scope of exposure assessment and type of risk characterisation required for man via the environment are described in the following table based on the hazard conclusions reported and justified in section 5.11.

Table 102. Type of risk characterisation required for man via the environment

Route of exposure and type of effects	Type of risk characterisation	Hazard conclusion (see section 5.11)
Inhalation: Systemic Long Term	Quantitative	DNEL (Derived No Effect Level) = 15 mg/m³
Oral: Systemic Long Term	Quantitative	DNEL (Derived No Effect Level) = 0.4 mg/kg bw/day

9.0.2.3. Workers

Scope and type of assessment

The scope of exposure assessment and type of risk characterisation required for workers are described in the following table based on the hazard conclusions presented in section 5.11.

Table 103. Type of risk characterisation required for workers

Route	Type of effect	Type of risk characterisation	Hazard conclusion (see section 5.11)
Inhalation	Systemic Long Term	Quantitative	DNEL (Derived No Effect Level) = 15 mg/m³
	Systemic Acute	Quantitative	DNEL (Derived No Effect Level) = 30 mg/m³
	Local Long Term	Quantitative	DNEL (Derived No Effect Level) = 15 mg/m³
	Local Acute	Quantitative	DNEL (Derived No Effect Level) = 30 mg/m³
Dermal	Systemic Long Term	Quantitative	DNEL (Derived No Effect Level) = 0.79 mg/kg bw/day
	Systemic Acute	Quantitative	DNEL (Derived No Effect Level) = 6.3 mg/kg bw/day
	Local Long Term	Quantitative	DNEL (Derived No Effect Level) = 267 µg/cm²
	Local Acute	Quantitative	DNEL (Derived No Effect Level) = 3.6E3 µg/cm²
Eye	Local	Qualitative	Low hazard (no threshold derived)

9.0.2.4. Consumers

Exposure assessment is not applicable as there are no consumer-related uses for the substance.

9.1. Exposure scenario 1: Manufacture - Manufacture of substance

Environment contributing scenario(s):	
Manufacture of substance	ERC 1
Worker contributing scenario(s):	
Use in closed process, no likelihood of exposure [Condition 1]	PROC 1
Use in closed process, no likelihood of exposure [Condition 2]	PROC 1
Use in closed, continuous process with occasional controlled exposure [Condition 1]	PROC 2
Use in closed, continuous process with occasional controlled exposure [Condition 2]	PROC 2
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 1]	PROC 8b
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 2]	PROC 8b
Use as laboratory reagent	PROC 15

Description of the technical process covered by the SpERC: ESVOC SpERC 1.1.v1

Process Categories: 1 (use in closed process, no likelihood of exposure), 2 (use in closed, continuous process with occasional controlled exposure), 3 (use in closed batch process (synthesis or formulation)), 4 (use in batch and other process (synthesis) where opportunity for exposure arises), 8a (transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities), 8b (transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities), 15 (use as laboratory reagent)

9.1.1. Environmental contributing scenario 1: Manufacture of substance

9.1.1.1. Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily use at site: **Confidential information**
• Annual use at a site: **Confidential information**
• Percentage of tonnage used at regional scale: **Confidential information**
Conditions and measures related to sewage treatment plant
• Municipal STP: Yes [Effectiveness Water: 87.37%]
• Discharge rate of STP: ≥ 2E4 m^3/d *Wastewater is treated by a specific STP which is run by InfraLeuna. The default value set by CHESAR amounts to 2000 m³/d which is associated with 10000 inhabitants. Since the STP of InfraLeuna is dimensioned for maximum 300000 inhabitants (http://www.infraleuna.de/standort-leuna/daten-und-fakten/), the discharge rate must be at least tenfold higher. As a consequence, a value of 20000 m³/d is assumed for this input parameter.*
• Application of the STP sludge on agricultural soil: No
Conditions and measures related to treatment of waste (including article waste)
• Particular considerations on the waste treatment operations: No (no waste) (No waste generated.)

Other conditions affecting environmental exposure
• Receiving surface water flow rate: ≤ 1.5E6 m^3/d *The effluent of the STP relevant for this Exposure Scenario is discharged into the river Saale. According to data of the German "Landesbetrieb für Hochwasserschutz und Wasserwirtschaft, Sachsen-Anhalt", the receiving surface water flow rate of the river Saale amounts at least to 18 m^3/s which refers to 1555200 m^3/d (http://www.hochwasservorhersage.sachsen-anhalt.de/wiskiwebpublic/stat_512034078.htm#W). As a consequence, exposure modelling takes 1500000 m^3/d for this input parameter into account.*

9.1.1.2. Releases

The local releases to the environment are reported in the following table.

Table 104. Local releases to the environment

Release	Release factor estimation method	Explanation / Justification
Water	SpERC based ESVOC SpERC 1.1.v1 - ESVOC SpERC 1.1.v1 Manufacture of substance - ESVOC SpERC 1.1.v1 (10)	**Initial release factor:** 1% **Final release factor:** 1% **Local release rate:** **Confidential information** **Explanation / Justification:** The justification for the release factor to water is provided by the SpERC factsheet "Manufacture of substance (industrial), version 1" as follows: Emission factors to wastewater are conservatively calculated from equipment cleaning and substance aqueous solubility. Assumption of 10 m3 of wastewater generated per 1 tonne of substance is conservative. Example: 1 mg/L x 10 m3/tonne use x 1000 L/m^3 x 1 tonne/10 x E9 mg = 0.00001 tonnes/tonne used. For WS range (e.g., 1-10 mg/L), the geometric mean (i.e., 3.2 mg/L) is used to calculate the fraction released.
Air	SpERC based same as above	**Initial release factor:** 1% **Final release factor:** 1% **Local release rate:** **Confidential information** **Explanation / Justification:** The justification for the release factor to air is provided by the SpERC factsheet "Manufacture of substance (industrial), version 1" as follows: EUTGD (2003), Appendix 1.
Soil	SpERC based same as above	**Final release factor:** 0.01% **Explanation / Justification:** The justification for the release factor to soil is provided by the SpERC factsheet "Manufacture of substance (industrial), version 1" as follows: ERC 1 default.

Further clarification for release factors (water, air)

The estimated release factors for this Exposure Scenario are based on the Operational Conditions (OCs) and the Risk Management Measures (RMMs) as listed below.

Operational Conditions

The process is optimized for highly efficient use of raw material which leads to a very minimal environmental release. The processes are performed without water contact. Wastewater emissions are only generated from equipment cleaning with water. Air emissions are negligible since most of the

processes operate in a contained system.

Risk Management Measures

No on-site technology for air emission reduction takes place (outdoor use). Due to the fact, that most of the processes are performed in contained systems, air emission reduction is not necessary.

Wastewater is treated by on-site STP which ensures a typical removal efficiency of at least 87 % as predicted by the simple treat model (Technical Guidance Document on Risk Assessment, Part II, 2003) and by CHESAR (v2.2). The wastewater treatment techniques are based on separation techniques (sedimentation, oil-water separation) and biological treatment techniques (aerobic/anaerobic digestion processes, nitrification/denitrification).

Releases to waste

Release factor to waste from the process: 0 %

No release to waste is described by ESVOC, SpERC 1.1.v1.

9.1.1.3. Exposure and risks for the environment and man via the environment

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 105. Exposure concentrations and risks for the environment

Protection target	Exposure concentration	Risk characterisation
Freshwater	**Local PEC:** 0.129 mg/L	RCR < 0.01
Sediment (freshwater)	**Local PEC:** 0.496 mg/kg dw	RCR < 0.01
Marine water	**Local PEC:** 0.095 mg/L	RCR = 0.032
Sediment (marine water)	**Local PEC:** 0.365 mg/kg dw	RCR = 0.032
Sewage treatment plant	**Local PEC:** 9.472 mg/L	RCR = 0.077
Agricultural soil	**Local PEC:** 0.028 mg/kg dw	RCR < 0.01
Man via Environment - Inhalation	**Local PEC:** 0.228 mg/m³	RCR = 0.015
Man via Environment - Oral	**Exposure via food consumption:** 0.054 mg/kg bw/day	RCR = 0.134
Man via environment - combined routes		RCR = 0.149

Table 106. Contribution to oral intake for man via the environment from local contribution

Type of food	Estimated daily dose	Concentration in food
Drinking water	0.004 mg/kg bw/day	0.153 mg/L
Fish	1.435E-4 mg/kg bw/day	0.087 mg/kg ww
Leaf crops	0.048 mg/kg bw/day	2.811 mg/kg ww
Root crops	7.827E-4 mg/kg bw/day	0.143 mg/kg ww
Meat	7.732E-7 mg/kg bw/day	1.798E-4 mg/kg ww
Milk	1.441E-5 mg/kg bw/day	0.002 mg/kg ww

Conclusion on risk characterisation

The results of the calculation with the given data show, that the manufacture of the substance with the

corresponding SpERC can be considered to be of acceptable risk for the environment, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.1.2. Worker contributing scenario 1: Use in closed process, no likelihood of exposure [Condition 1] (PROC 1)

9.1.2.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed system (minimal contact during routine operations)	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 140 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.1.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 107. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.007 mg/kg bw/day** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.002 mg/cm²** (TRA Worker v3)	RCR < 0.01
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.011
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.1.3. Worker contributing scenario 2: Use in closed process, no likelihood of exposure [Condition 2] (PROC 1)

9.1.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR*	TRA Worker v3

	Method
(submitted February 2014) for further information regarding vapour pressure extrapolation.	
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• Containment: Closed system (minimal contact during routine operations)	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Outdoor	TRA Worker v3
• Process temperature (for liquid): ≤ 150 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.1.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 108. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.021 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.085 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.021 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.085 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.007 mg/kg bw/day** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.002 mg/cm²** (TRA Worker v3)	RCR < 0.01
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.01
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding

PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.1.4. Worker contributing scenario 3: Use in closed, continuous process with occasional controlled exposure [Condition 1] (PROC 2)

9.1.4.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• Containment: Closed continuous process with occasional controlled exposure	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Outdoor	TRA Worker v3
• Process temperature (for liquid): ≤ 150 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.1.4.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 109. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**3.198 mg/m³** (TRA Worker v3)	RCR = 0.213
Inhalation, systemic, acute	**21.32 mg/m³** (TRA Worker v3)	RCR = 0.711
Inhalation, local, long-term	**3.198 mg/m³** (TRA Worker v3)	RCR = 0.213
Inhalation, local, acute	**21.32 mg/m³** (TRA Worker v3)	RCR = 0.711
Dermal, systemic, long-term	**0.041 mg/kg bw/day** (TRA Worker v3)	RCR = 0.052
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.006 mg/cm²** (TRA Worker v3)	RCR = 0.022
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.265
Combined routes, systemic, acute		RCR = 0.711 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.1.5. Worker contributing scenario 4: Use in closed, continuous process with occasional controlled exposure [Condition 2] (PROC 2)

9.1.5.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• Containment: Closed continuous process with occasional controlled exposure	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3

	Method
Other conditions affecting workers exposure	
• Place of use: Outdoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.1.5.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 110. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.279 mg/m³** (TRA Worker v3)	RCR = 0.085
Inhalation, systemic, acute	**8.528 mg/m³** (TRA Worker v3)	RCR = 0.284
Inhalation, local, long-term	**1.279 mg/m³** (TRA Worker v3)	RCR = 0.085
Inhalation, local, acute	**8.528 mg/m³** (TRA Worker v3)	RCR = 0.284
Dermal, systemic, long-term	**0.068 mg/kg bw/day** (TRA Worker v3)	RCR = 0.087
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.037
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.172
Combined routes, systemic, acute		RCR = 0.284 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.1.6. Worker contributing scenario 5: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 1] (PROC 8b)

9.1.6.1. Conditions of use

	Method
Product (article) characteristics	

	Method
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	TRA Worker v3
Technical and organisational conditions and measures	
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Outdoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.1.6.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 111. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.213 mg/m³** (TRA Worker v3)	RCR = 0.014
Inhalation, systemic, acute	**4.264 mg/m³** (TRA Worker v3)	RCR = 0.142
Inhalation, local, long-term	**0.213 mg/m³** (TRA Worker v3)	RCR = 0.014
Inhalation, local, acute	**4.264 mg/m³** (TRA Worker v3)	RCR = 0.142
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Worker v3)	RCR = 0.868
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.882
Combined routes, systemic, acute		RCR = 0.142 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding

PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.1.7. Worker contributing scenario 6: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 2] (PROC 8b)

9.1.7.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25%	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Outdoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.1.7.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 112. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**3.837 mg/m³** (TRA Workers 3.0)	RCR = 0.256
Inhalation, systemic, acute	**25.58 mg/m³** (TRA Workers 3.0)	RCR = 0.853
Inhalation, local, long-term	**3.837 mg/m³** (TRA Workers 3.0)	RCR = 0.256
Inhalation, local, acute	**25.58 mg/m³** (TRA Workers 3.0)	RCR = 0.853
Dermal, systemic, long-term	**0.411 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.521
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.03 mg/cm²** (TRA Workers 3.0)	RCR = 0.112
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Combined routes, systemic, long-term		RCR = 0.777
Combined routes, systemic, acute		RCR = 0.853 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data estimate a potential risk for workers. However, measured workplace concentrations are available which are assessed in a higher TIER risk assessment (please refer to section 9a.1.1). These data identify an acceptable risk for workers (RCR < 1) referring to transfer processes which are performed outdoor.

9.1.8. Worker contributing scenario 7: Use as laboratory reagent (PROC 15)

9.1.8.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.1.8.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 113. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, systemic, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Dermal, systemic, long-term	**0.068 mg/kg bw/day** (TRA Worker v3)	RCR = 0.086
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.02 mg/cm²** (TRA Worker v3)	RCR = 0.074
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.188
Combined routes, systemic, acute		RCR = 0.203 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.2. Exposure scenario 2: Formulation - Formulation of substance

Environment contributing scenario(s):	
Formulation in materials	ERC 2
Worker contributing scenario(s):	
Use in closed process, no likelihood of exposure	PROC 1
Use in closed, continuous process with occasional controlled exposure	PROC 2
Use in closed batch process (synthesis or formulation)	PROC 3
Use in batch and other process (synthesis) where opportunity for exposure arises	PROC 4
Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)	PROC 5
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities	PROC 8a
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities	PROC 8b
Transfer of substance or preparation into small containers (dedicated filling line, including weighing)	PROC 9
Use as laboratory reagent	PROC 15

Description of the technical process covered by the SpERC: ESVOC SpERC 2.2.v1

Scope of used SpERC: Formulation, packing and re-packing of the substance and its mixtures in batch or continuous operations, including storage, materials transfers, mixing, tabletting, compression, pelletisation, extrusion, large and small scale packing, sampling, maintenance and associated laboratory activities.

9.2.1. Environmental contributing scenario 1: Formulation in materials

9.2.1.1. Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily use at site: **Confidential information**
• Annual use at a site: **Confidential information**
• Percentage of tonnage used at regional scale: **Confidential information**
Conditions and measures related to sewage treatment plant
• Municipal STP: Yes [Effectiveness Water: 87.37 %]
• Discharge rate of STP: ≥ 2E3 m^3/d
• Application of the STP sludge on agricultural soil: No
Conditions and measures related to treatment of waste (including article waste)
• Particular considerations on the waste treatment operations: No (low risk) (ERC based assessment demonstrating control of risk with default conditions. Low risk assumed for waste life stage. Waste disposal according to national/local legislation is sufficient.)
Other conditions affecting environmental exposure
• Receiving surface water flow rate: ≥ 1.8E4 m^3/d

9.2.1.2. Releases

The local releases to the environment are reported in the following table.

Table 114. Local releases to the environment

Release	Release factor estimation method	Explanation / Justification
Water	SpERC based ESVOC SpERC 2.2.v1 - ESVOC SpERC 2.2.v1 (4) Formulation & (re)packing of substances and mixtures (industrial): solvent-borne - Formulation & packing of preparations and mixtures	**Initial release factor:** 0.5 % **Final release factor:** 0.5 % **Local release rate:** **Confidential information** **Explanation / Justification:** Justification is given by ESVOC SpERC fact sheet (Formulation & (re)packing of substances and mixtures V1) as follows: Emission factors to wastewater are conservatively calculated based on wastewater volume generated from cleaning operations and substance aqueous solubility. Assumption of 5 m^3 of wastewater generated per 1 tonne of substance used is relatively conservative. Example: 1 mg/L x 5 m^3/tonne use x 1000 L/m^3 x 1 tonne/10xE9 mg = 0.000005 tonnes/tonne used. For WS range (e.g., 1-10 mg/L), the geometric mean (i.e., 3.2 mg/L) is used to calculate the fraction released. OECD Coatings ESD reports no releases of volatile substances to water. The values used here are consistent with those reported for dust.
Air	SpERC based same as above	**Initial release factor:** 1 % **Final release factor:** 1 % **Local release rate:** **Confidential information** **Explanation / Justification:** Justification is given by ESVOC SpERC fact sheet (Formulation & (re)packing of substances and mixtures V1) as follows: Estimates on the basis of substance vapour pressure taken from EUTGD (2003) Appendix 1. These values are consistent with the range of emissions reported in OECD Coatings ESD and consistent with EU Solvent Emissions Directive after typical RMMs as further documented in Coatings SpERC fact sheet.
Soil	SpERC based same as above	**Final release factor:** 0.01 % **Explanation / Justification:** Justification is given by ESVOC SpERC fact sheet (Formulation & (re)packing of substances and mixtures V1) as follows: ERC2 default.

Further clarification for release factors (water, air)

The estimated release factors for this Exposure Scenario are based on the Operational Conditions (OCs) and the Risk Management Measures (RMMs) as listed below.

Operational Conditions

Indoor use is described here. The process is optimized for highly efficient use of raw material which leads to a very minimal environmental release. The processes are performed without water contact. Wastewater emissions are only generated from equipment cleaning with water. Since the substance is considered as volatile, air emission controls take place.

Risk Management Measures

On-site technology for air emission reduction takes place. Appropriate air removal techniques to achieve the required emission reduction are listed below.

- Wet scrubber (gas removal): typical efficiency of 70 %
- Thermal oxidation: typical efficiency of 98 %
- Vapour recovery (adsorption): typical efficiency of 80 %

Wastewater is treated by on-site and/or off-site STP which ensures a typical removal efficiency of at least 87 % as predicted by the simple treat model (Technical Guidance Document on Risk Assessment, Part II, 2003) and by CHESAR (v2.2). The wastewater treatment techniques are based on separation techniques (sedimentation, oil-water separation) and biological treatment techniques (aerobic/anaerobic digestion processes, nitrification/denitrification).

Releases to waste

Release factor to waste from the process: 0 %

No initial release to waste is given.

9.2.1.3. Exposure and risks for the environment and man via the environment

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 115. Exposure concentrations and risks for the environment

Protection target	Exposure concentration	Risk characterisation
Freshwater	**Local PEC:** 3.162 mg/L	RCR = 0.105
Sediment (freshwater)	**Local PEC:** 12.14 mg/kg dw	RCR = 0.105
Marine water	**Local PEC:** 0.316 mg/L	RCR = 0.105
Sediment (marine water)	**Local PEC:** 1.214 mg/kg dw	RCR = 0.105
Sewage treatment plant	**Local PEC:** 31.57 mg/L	RCR = 0.257
Agricultural soil	**Local PEC:** 0.028 mg/kg dw	RCR < 0.01
Man via Environment - Inhalation	**Local PEC:** 0.228 mg/m³	RCR = 0.015
Man via Environment - Oral	**Exposure via food consumption:** 0.128 mg/kg bw/day	RCR = 0.321
Man via environment - combined routes		RCR = 0.336

Table 116. Contribution to oral intake for man via the environment from local contribution

Type of food	Estimated daily dose	Concentration in food
Drinking water	0.074 mg/kg bw/day	2.6 mg/L
Fish	0.005 mg/kg bw/day	3.12 mg/kg ww
Leaf crops	0.048 mg/kg bw/day	2.811 mg/kg ww
Root crops	7.824E-4 mg/kg bw/day	0.143 mg/kg ww
Meat	1.233E-6 mg/kg bw/day	2.867E-4 mg/kg ww
Milk	2.298E-5 mg/kg bw/day	0.003 mg/kg ww

Conclusion on risk characterisation

The results of the calculation with the given data show, that the industrial formulation of the substance with the corresponding SpERC can be considered to be of acceptable risk for the environment, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.2.2. Worker contributing scenario 1: Use in closed process, no likelihood of exposure (PROC 1)

9.2.2.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed system (minimal contact during routine operations)	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.2.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 117. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.007 mg/kg bw/day** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.002 mg/cm²** (TRA Worker v3)	RCR < 0.01
Dermal, local, acute		Qualitative (see below)

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.011
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.2.3. Worker contributing scenario 2: Use in closed, continuous process with occasional controlled exposure (PROC 2)

9.2.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed continuous process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.2.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 118. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, systemic, acute	**12.18 mg/m³** (TRA Worker v3)	RCR = 0.406
Inhalation, local, long-term	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, acute	**12.18 mg/m³** (TRA Worker v3)	RCR = 0.406
Dermal, systemic, long-term	**0.068 mg/kg bw/day** (TRA Worker v3)	RCR = 0.087
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.037
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.29
Combined routes, systemic, acute		RCR = 0.406 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.2.4. Worker contributing scenario 3: Use in closed batch process (synthesis or formulation) (PROC 3)

9.2.4.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 2.532E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3

	Method
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 50 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.2.4.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 119. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, systemic, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Worker v3)	RCR = 0.044
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.038
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.145
Combined routes, systemic, acute		RCR = 0.203 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.2.5. Worker contributing scenario 4: Use in batch and other process (synthesis) where

opportunity for exposure arises (PROC 4)

9.2.5.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.2.5.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 120. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, systemic, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, local, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Dermal, systemic, long-term	**0.343 mg/kg bw/day** (TRA Worker v3)	RCR = 0.434
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.495
Combined routes, systemic, acute		RCR = 0.203 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.2.6. Worker contributing scenario 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) (PROC 5)

9.2.6.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25%	TRA Worker v3
• Vapour pressure at elevated temperature: < 2.532E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 50 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.2.6.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 121. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.914 mg/m³** (TRA Workers 3.0)	RCR = 0.061
Inhalation, systemic, acute	**3.655 mg/m³** (TRA Workers 3.0)	RCR = 0.122
Inhalation, local, long-term	**0.914 mg/m³** (TRA Workers 3.0)	RCR = 0.061
Inhalation, local, acute	**3.655 mg/m³** (TRA Workers 3.0)	RCR = 0.122
Dermal, systemic, long-term	**0.411 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.521
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.06 mg/cm²** (TRA Workers 3.0)	RCR = 0.225
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.582
Combined routes, systemic, acute		RCR = 0.122 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.2.7. Worker contributing scenario 6: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities (PROC 8a)

9.2.7.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25%	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	

	Method
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.2.7.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 122. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.827 mg/m³** (TRA Workers 3.0)	RCR = 0.122
Inhalation, systemic, acute	**7.309 mg/m³** (TRA Workers 3.0)	RCR = 0.244
Inhalation, local, long-term	**1.827 mg/m³** (TRA Workers 3.0)	RCR = 0.122
Inhalation, local, acute	**7.309 mg/m³** (TRA Workers 3.0)	RCR = 0.244
Dermal, systemic, long-term	**0.411 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.521
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.03 mg/cm²** (TRA Workers 3.0)	RCR = 0.112
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.643
Combined routes, systemic, acute		RCR = 0.244 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.2.8. Worker contributing scenario 7: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b)

9.2.8.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25%	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 95 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.2.8.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 123. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.457 mg/m³** (TRA Workers 3.0)	RCR = 0.03
Inhalation, systemic, acute	**1.827 mg/m³** (TRA Workers 3.0)	RCR = 0.061
Inhalation, local, long-term	**0.457 mg/m³** (TRA Workers 3.0)	RCR = 0.03
Inhalation, local, acute	**1.827 mg/m³** (TRA Workers 3.0)	RCR = 0.061
Dermal, systemic, long-term	**0.411 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.521
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.03 mg/cm²** (TRA Workers 3.0)	RCR = 0.112
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.551
Combined routes, systemic, acute		RCR = 0.061 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.2.9. Worker contributing scenario 8: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) (PROC 9)

9.2.9.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.2.9.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 124. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, systemic, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, local, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Dermal, systemic, long-term	**0.343 mg/kg bw/day** (TRA Worker v3)	RCR = 0.434
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.536
Combined routes, systemic, acute		RCR = 0.203 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.2.10. Worker contributing scenario 9: Use as laboratory reagent (PROC 15)

9.2.10.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 4.427E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness	TRA Worker v3

	Method
Inhal: 95 %]	
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 60 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.2.10.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 125. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, systemic, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Dermal, systemic, long-term	**0.017 mg/kg bw/day** (TRA Worker v3)	RCR = 0.022
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.005 mg/cm²** (TRA Worker v3)	RCR = 0.019
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.123
Combined routes, systemic, acute		RCR = 0.203 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3. Exposure scenario 3: Use at industrial site - Industrial use for the production of fine chemicals

Sector of use:
SU 8, Manufacture of bulk, large scale chemicals (including petroleum products) (SU 3: Industrial use)
SU 9, Manufacture of fine chemicals (SU 3: Industrial use)
SU 17, General manufacturing, e.g. machinery, equipment, vehicles, other transport equipment. (SU 3: Industrial use)
SU 0, Other (SU 3: Industrial use)

Environment contributing scenario(s):	
Industrial use of processing aids in processes and products, not becoming part of articles	ERC 4
Industrial use resulting in manufacture of another substance (use of intermediates)	ERC 6a
Industrial use of reactive processing aids	ERC 6b
Industrial use of sub-stances in closed systems	ERC 7
Worker contributing scenario(s):	
Use in closed process, no likelihood of exposure [Condition 1]	PROC 1
Use in closed process, no likelihood of exposure [Condition 2]	PROC 1
Use in closed, continuous process with occasional controlled exposure [Condition 1]	PROC 2
Use in closed, continuous process with occasional controlled exposure [Condition 2]	PROC 2
Use in closed batch process (synthesis or formulation) [Condition 1]	PROC 3
Use in closed batch process (synthesis or formulation) [Condition 2]	PROC 3
Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 1]	PROC 4
Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 2]	PROC 4
Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 3]	PROC 4
Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)	PROC 5
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 1]	PROC 8a
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 2]	PROC 8a
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 1]	PROC 8b
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 2]	PROC 8b
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 3]	PROC 8b
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 4]	PROC 8b
Transfer of substance or preparation into small containers (dedicated filling line,	PROC 9

including weighing)	
Production of preparations or articles by tabletting, compression, extrusion, pelletisation	PROC 14
Use as laboratory reagent [Condition 1]	PROC 15
Use as laboratory reagent [Condition 2]	PROC 15
Hand-mixing with intimate contact and only PPE available	*PROC 19**

*PROC 19 is included in the uses advised against.

9.3.1. Environmental contributing scenario 1: Industrial use of processing aids in processes and products, not becoming part of articles

9.3.1.1. Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily use at site: **Confidential information**
• Annual use at a site: **Confidential information**
• Percentage of tonnage used at regional scale: **Confidential information**
Conditions and measures related to sewage treatment plant
• Municipal STP: Yes [Effectiveness Water: 87.37 %]
• Discharge rate of STP: ≥ 2E3 m^3/d
• Application of the STP sludge on agricultural soil: No
Conditions and measures related to treatment of waste (including article waste)
• Particular considerations on the waste treatment operations: No (low risk) (ERC based assessment demonstrating control of risk with default conditions. Low risk assumed for waste life stage. Waste disposal according to national/local legislation is sufficient.)
Other conditions affecting environmental exposure
• Receiving surface water flow rate: ≥ 1.8E4 m^3/d

9.3.1.2. Releases

With regard to the market data, different Environmental Release Categories were declared as relevant to this Exposure Scenario. The Use Descriptors ERC4, ERC 6a, ERC 6b and ERC 7 were provided by different Downstream Users to account for this Identified Use. In order to assess all of these Categories, the most critical release factor for each environmental compartment was assumed. Nevertheless, the release factor to water (100 %) and the release factor to air (100 %) as defined by ERC 4 were modified according to SpERC ESVOC 4.5a.v1. These release factors are still more critical than the relevant release factors defined by ERC 6a, ERC 6b and ERC 7.

The local releases to the environment are reported in the following table.

Table 126. Local releases to the environment

Release	Release factor estimation method	Explanation / Justification
Water	Release factor (SpERC 4.5a.v1 (release to water))	**Initial release factor:** 7% **Final release factor:** 7% **Local release rate:** **Confidential information** **Explanation / Justification:** Environmental release to water is most critical as defined by ERC 4 (100 %).

Release	Release factor estimation method	Explanation / Justification
		However, this release factor is considered as highly overestimated due to the given Operational Conditions (OCs) and Risk Management Measures (RMMs). As a consequence, SpERC ESVOC 4.5a.v1 was applied which takes 7 % release to water for the relevant solubility range into consideration.
Air	Release factor (SpERC 4.5a.v1 (release to air))	**Initial release factor:** 50% **Final release factor:** 50% **Local release rate:** **Confidential information** **Explanation / Justification:** Environmental release to air is most critical as defined by ERC 4 (100 %). However, this release factor is considered as highly overestimated due to the given Operational Conditions (OCs) and Risk Management Measures (RMMs). As a consequence, SpERC ESVOC 4.5a.v1 was applied which takes 50 % release to air for the relevant vapour pressure range into consideration.
Soil	Release factor (ERC 7 (default release to soil))	**Final release factor:** 5% **Explanation / Justification:** With regard to environmental releases to soil, ERC 4 and ERC 7 describe the most critical release (5 %).

Further clarification for release factors (water, air)

The estimated release factors for this Exposure Scenario are based on the Operational Conditions (OCs) and the Risk Management Measures (RMMs) as listed below.

Operational Conditions

The process is optimized for highly efficient use of raw material which leads to a very minimal environmental release. The processes are performed without water contact. Wastewater emissions are only generated from equipment cleaning with water.

Risk Management Measures

On-site technology for air emission reduction takes place for indoor applications. Appropriate air removal techniques to achieve the required emission reduction are listed below.

- Wet scrubber (gas removal): typical efficiency of 70 %
- Thermal oxidation: typical efficiency of 98 %
- Vapour recovery (adsorption): typical efficiency of 80 %

Wastewater is treated by on-site and/or off-site STP which ensures a typical removal efficiency of at least 87 % as predicted by the simple treat model (Technical Guidance Document on Risk Assessment, Part II, 2003) and by CHESAR (v2.2). The wastewater treatment techniques are based on separation techniques (sedimentation, oil-water separation) and biological treatment techniques (aerobic/anaerobic digestion processes, nitrification/denitrification).

Releases to waste

Release factor to waste from the process: 0 %

No initial release to waste is given.

9.3.1.3. Exposure and risks for the environment and man via the environment

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 127. Exposure concentrations and risks for the environment

Protection target	Exposure concentration	Risk characterisation
Freshwater	**Local PEC:** 3.209 mg/L	RCR = 0.107
Sediment (freshwater)	**Local PEC:** 12.32 mg/kg dw	RCR = 0.107
Marine water	**Local PEC:** 0.321 mg/L	RCR = 0.107
Sediment (marine water)	**Local PEC:** 1.232 mg/kg dw	RCR = 0.107
Sewage treatment plant	**Local PEC:** 32.05 mg/L	RCR = 0.26
Agricultural soil	**Local PEC:** 0.096 mg/kg dw	RCR < 0.01
Man via Environment - Inhalation	**Local PEC:** 0.828 mg/m³	RCR = 0.055
Man via Environment - Oral	**Exposure via food consumption:** 0.258 mg/kg bw/day	RCR = 0.645
Man via environment - combined routes		RCR = 0.7

Table 128. Contribution to oral intake for man via the environment from local contribution

Type of food	Estimated daily dose	Concentration in food
Drinking water	0.075 mg/kg bw/day	2.639 mg/L
Fish	0.005 mg/kg bw/day	3.166 mg/kg ww
Leaf crops	0.175 mg/kg bw/day	10.19 mg/kg ww
Root crops	0.003 mg/kg bw/day	0.494 mg/kg ww
Meat	3.194E-6 mg/kg bw/day	7.428E-4 mg/kg ww
Milk	5.953E-5 mg/kg bw/day	0.007 mg/kg ww

Conclusion on risk characterisation

The results of the calculation with the given data show, that the industrial use of the substance with the corresponding release factors can be considered to be of acceptable risk for the environment, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.2. Worker contributing scenario 1: Use in closed process, no likelihood of exposure [Condition 1] (PROC 1)

9.3.2.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3

	Method
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed system (minimal contact during routine operations)	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.3.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 129. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.007 mg/kg bw/day** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.002 mg/cm²** (TRA Worker v3)	RCR < 0.01
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.011
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at

least equivalent levels.

9.3.3. Worker contributing scenario 2: Use in closed process, no likelihood of exposure [Condition 2] (PROC 1)

9.3.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed system (minimal contact during routine operations)	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 150 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.3.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 130. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic,	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01

Route of exposure and type of effects	Exposure concentration	Risk characterisation
long-term		
Inhalation, systemic, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.007 mg/kg bw/day** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.002 mg/cm²** (TRA Worker v3)	RCR < 0.01
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.011
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.4. Worker contributing scenario 3: Use in closed, continuous process with occasional controlled exposure [Condition 1] (PROC 2)

9.3.4.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed continuous process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3

	Method
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.3.4.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 131. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, systemic, acute	**12.18 mg/m³** (TRA Worker v3)	RCR = 0.406
Inhalation, local, long-term	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, acute	**12.18 mg/m³** (TRA Worker v3)	RCR = 0.406
Dermal, systemic, long-term	**0.068 mg/kg bw/day** (TRA Worker v3)	RCR = 0.087
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.037
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.29
Combined routes, systemic, acute		RCR = 0.406 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.5. Worker contributing scenario 4: Use in closed, continuous process with occasional controlled exposure [Condition 2] (PROC 2)

9.3.5.1. Conditions of use

	Method
Product (article) characteristics	

	Method
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• Containment: Closed continuous process with occasional controlled exposure	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Outdoor	TRA Worker v3
• Process temperature (for liquid): ≤ 170 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.3.5.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 132. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**5.33 mg/m³** (TRA Worker v3)	RCR = 0.355
Inhalation, systemic, acute	**21.32 mg/m³** (TRA Worker v3)	RCR = 0.711
Inhalation, local, long-term	**5.33 mg/m³** (TRA Worker v3)	RCR = 0.355
Inhalation, local, acute	**21.32 mg/m³** (TRA Worker v3)	RCR = 0.711
Dermal, systemic, long-term	**0.068 mg/kg bw/day** (TRA Worker v3)	RCR = 0.087
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.037

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.442
Combined routes, systemic, acute		RCR = 0.711 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.6. Worker contributing scenario 5: Use in closed batch process (synthesis or formulation) [Condition 1] (PROC 3)

9.3.6.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.3.6.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 133. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, systemic, acute	**3.655 mg/m³** (TRA Worker v3)	RCR = 0.122
Inhalation, local, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, local, acute	**3.655 mg/m³** (TRA Worker v3)	RCR = 0.122
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Worker v3)	RCR = 0.044
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.038
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.105
Combined routes, systemic, acute		RCR = 0.122 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.7. Worker contributing scenario 6: Use in closed batch process (synthesis or formulation) [Condition 2] (PROC 3)

9.3.7.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the*	TRA Worker v3

	Method
exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.	
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 160 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.3.7.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 134. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, systemic, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Worker v3)	RCR = 0.044
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.038
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.145
Combined routes, systemic, acute		RCR = 0.203 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.8. Worker contributing scenario 7: Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 1] (PROC 4)

9.3.8.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.3.8.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 135. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, systemic, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Dermal, systemic, long-term	**0.343 mg/kg bw/day** (TRA Worker v3)	RCR = 0.434
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.536
Combined routes, systemic, acute		RCR = 0.203 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.9. Worker contributing scenario 8: Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 2] (PROC 4)

9.3.9.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 2.532E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 15 minutes	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness	TRA Worker v3

	Method
Inhal: 95 %]	
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 50 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.3.9.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 136. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.02
Inhalation, systemic, acute	**12.18 mg/m³** (TRA Worker v3)	RCR = 0.406
Inhalation, local, long-term	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.02
Inhalation, local, acute	**12.18 mg/m³** (TRA Worker v3)	RCR = 0.406
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Worker v3)	RCR = 0.043
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.005 mg/cm²** (TRA Worker v3)	RCR = 0.019
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.064
Combined routes, systemic, acute		RCR = 0.406 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.10. Worker contributing scenario 9: Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 3] (PROC 4)

9.3.10.1. Conditions of use

	Method
Product (article) characteristics	

	Method
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 160 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.3.10.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 137. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.02
Inhalation, systemic, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, long-term	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.02
Inhalation, local, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Dermal, systemic, long-term	**0.069 mg/kg bw/day** (TRA Worker v3)	RCR = 0.087

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.037
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.107
Combined routes, systemic, acute		RCR = 0.203 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.11. Worker contributing scenario 10: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) (PROC 5)

9.3.11.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25%	TRA Worker v3
• Vapour pressure at elevated temperature: < 7.491E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3

	Method
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 70 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.3.11.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 138. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.914 mg/m³** (TRA Workers 3.0)	RCR = 0.061
Inhalation, systemic, acute	**3.655 mg/m³** (TRA Workers 3.0)	RCR = 0.122
Inhalation, local, long-term	**0.914 mg/m³** (TRA Workers 3.0)	RCR = 0.061
Inhalation, local, acute	**3.655 mg/m³** (TRA Workers 3.0)	RCR = 0.122
Dermal, systemic, long-term	**0.411 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.521
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.06 mg/cm²** (TRA Workers 3.0)	RCR = 0.225
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.582
Combined routes, systemic, acute		RCR = 0.122 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.12. Worker contributing scenario 11: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 1] (PROC 8a)

9.3.12.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25%	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.3.12.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 139. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.914 mg/m³** (TRA Workers 3.0)	RCR = 0.061
Inhalation, systemic, acute	**3.655 mg/m³** (TRA Workers 3.0)	RCR = 0.122
Inhalation, local, long-term	**0.914 mg/m³** (TRA Workers 3.0)	RCR = 0.061
Inhalation, local, acute	**3.655 mg/m³** (TRA Workers 3.0)	RCR = 0.122
Dermal, systemic, long-term	**0.411 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.521
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.03 mg/cm²** (TRA Workers 3.0)	RCR = 0.112
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.582
Combined routes, systemic, acute		RCR = 0.122 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.13. Worker contributing scenario 12: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 2] (PROC 8a)

9.3.13.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 2.532E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 50 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.3.13.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 140. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.371 mg/m³** (TRA Worker v3)	RCR = 0.091
Inhalation, systemic, acute	**9.137 mg/m³** (TRA Worker v3)	RCR = 0.305
Inhalation, local, long-term	**1.371 mg/m³** (TRA Worker v3)	RCR = 0.091
Inhalation, local, acute	**9.137 mg/m³** (TRA Worker v3)	RCR = 0.305
Dermal, systemic, long-term	**0.411 mg/kg bw/day** (TRA Worker v3)	RCR = 0.521
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.03 mg/cm²** (TRA Worker v3)	RCR = 0.112
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.612
Combined routes, systemic, acute		RCR = 0.305 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.14. Worker contributing scenario 13: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 1] (PROC 8b)

9.3.14.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25%	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	

	Method
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.3.14.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 141. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.457 mg/m³** (TRA Workers 3.0)	RCR = 0.03
Inhalation, systemic, acute	**1.827 mg/m³** (TRA Workers 3.0)	RCR = 0.061
Inhalation, local, long-term	**0.457 mg/m³** (TRA Workers 3.0)	RCR = 0.03
Inhalation, local, acute	**1.827 mg/m³** (TRA Workers 3.0)	RCR = 0.061
Dermal, systemic, long-term	**0.411 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.521
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.03 mg/cm²** (TRA Workers 3.0)	RCR = 0.112
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.551
Combined routes, systemic, acute		RCR = 0.061 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.15. Worker contributing scenario 14: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 2] (PROC 8b)

9.3.15.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	TRA Worker v3
Technical and organisational conditions and measures	
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Outdoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.3.15.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 142. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.213 mg/m³** (TRA Worker v3)	RCR = 0.014
Inhalation, systemic, acute	**4.264 mg/m³** (TRA Worker v3)	RCR = 0.142
Inhalation, local, long-term	**0.213 mg/m³** (TRA Worker v3)	RCR = 0.014
Inhalation, local, acute	**4.264 mg/m³** (TRA Worker v3)	RCR = 0.142
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Worker v3)	RCR = 0.868
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.882
Combined routes, systemic, acute		RCR = 0.142 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be

worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.16. Worker contributing scenario 15: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 3] (PROC 8b)

9.3.16.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	TRA Worker v3
Technical and organisational conditions and measures	
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 80 %]	Manual calculation
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Outdoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.3.16.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 143. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**2.132 mg/m³** (TRA Worker v3) Manual modification: **2.132 mg/m³ x 0.2 = 0.426 mg/m³**	RCR = 0.028
Inhalation, systemic, acute	**42.64 mg/m³** (TRA Worker v3) Manual modification: **42.64 mg/m³ x 0.2 = 8.528 mg/m³**	RCR = 0.284

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, local, long-term	**2.132 mg/m³** (TRA Worker v3) Manual modification: **2.132 mg/m³ x 0.2 = 0.426 mg/m³**	RCR = 0.028
Inhalation, local, acute	**42.64 mg/m³** (TRA Worker v3) Manual modification: **42.64 mg/m³ x 0.2 = 8.528 mg/m³**	RCR = 0.286
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Worker v3)	RCR = 0.868
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.896
Combined routes, systemic, acute		RCR = 0.286 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

Additional Risk Management Measures need to be considered for this process since Local Exhaust Ventilation (LEV) is applied. However, LEV cannot be adequately implemented in the modelling tool for outdoor applications. As a consequence, an additional inhalation exposure reduction of 80 % (reduction factor of 0.2) is manually applied.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.17. Worker contributing scenario 16: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 4] (PROC 8b)

9.3.17.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3

	Method
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 95 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.3.17.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 144. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.152 mg/m³** (TRA Worker v3)	RCR = 0.01
Inhalation, systemic, acute	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, long-term	**0.152 mg/m³** (TRA Worker v3)	RCR = 0.01
Inhalation, local, acute	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.102
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Worker v3)	RCR = 0.868
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.878
Combined routes, systemic, acute		RCR = 0.102 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.18. Worker contributing scenario 17: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) (PROC 9)

9.3.18.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.3.18.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 145. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.761 mg/m³** (TRA Worker v3)	RCR = 0.051
Inhalation, systemic, acute	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, long-term	**0.761 mg/m³** (TRA Worker v3)	RCR = 0.051
Inhalation, local, acute	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.102
Dermal, systemic, long-term	**0.343 mg/kg bw/day** (TRA Worker v3)	RCR = 0.434
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.485
Combined routes, systemic,		RCR = 0.102 (only based on

Route of exposure and type of effects	Exposure concentration	Risk characterisation
acute		acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.19. Worker contributing scenario 18: Production of preparations or articles by tabletting, compression, extrusion, pelletisation (PROC 14)

9.3.19.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.3.19.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 146. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.761 mg/m³** (TRA Worker v3)	RCR = 0.051
Inhalation, systemic, acute	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, long-term	**0.761 mg/m³** (TRA Worker v3)	RCR = 0.051
Inhalation, local, acute	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.102
Dermal, systemic, long-term	**0.172 mg/kg bw/day** (TRA Worker v3)	RCR = 0.217
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.025 mg/cm²** (TRA Worker v3)	RCR = 0.094
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.268
Combined routes, systemic, acute		RCR = 0.102 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.20. Worker contributing scenario 19: Use as laboratory reagent [Condition 1] (PROC 15)

9.3.20.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	

	Method
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.3.20.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 147. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.023 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.091 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.023 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.091 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.017 mg/kg bw/day** (TRA Worker v3)	RCR = 0.022
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.005 mg/cm²** (TRA Worker v3)	RCR = 0.019
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.023
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.21. Worker contributing scenario 20: Use as laboratory reagent [Condition 2] (PROC 15)

9.3.21.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 155 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.3.21.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 148. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, systemic, acute	**18.27 mg/m³** (TRA Worker v3)	RCR = 0.609
Inhalation, local, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, local, acute	**18.27 mg/m³** (TRA Worker v3)	RCR = 0.609

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Dermal, systemic, long-term	**0.003 mg/kg bw/day** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**9.917E-4 mg/cm²** (TRA Worker v3)	RCR < 0.01
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.065
Combined routes, systemic, acute		RCR = 0.609 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.3.22. Worker contributing scenario 21: Hand-mixing with intimate contact and only PPE available (PROC 19)

9.3.22.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3

	Method
• Skin surface potentially exposed: Two hands and forearms (1980 cm^2)	TRA Worker v3

9.3.22.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 149. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.827 mg/m³** (TRA Worker v3)	RCR = 0.122
Inhalation, systemic, acute	**12.18 mg/m³** (TRA Worker v3)	RCR = 0.406
Inhalation, local, long-term	**1.827 mg/m³** (TRA Worker v3)	RCR = 0.122
Inhalation, local, acute	**12.18 mg/m³** (TRA Worker v3)	RCR = 0.406
Dermal, systemic, long-term	**7.072 mg/kg bw/day** (TRA Worker v3)	RCR = 8.951 >>>**CAUTION:** Risk not controlled <<<
Dermal, systemic, acute		>>>**CAUTION:** Risk not controlled <<<
Dermal, local, long-term	**0.25 mg/cm²** (TRA Worker v3)	RCR = 0.936
Dermal, local, acute		Covered by long-term effect (dermal, local, long-term)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 9.073
Combined routes, systemic, acute		RCR = 0.406 (only based on acute inhalation)

Conclusion on risk characterisation

Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC bears a potential risk for workers. Even with specified Risk Management Measures (application of chemically resistant gloves conforming to EN374 with specific activity training), unsafe use is demonstrated.
In conclusion, PROC 19 is included in the uses advised against.

9.4. Exposure scenario 4: Use at industrial site - Industrial use for the production of pharmaceuticals

Sector of use:
SU 8, Manufacture of bulk, large scale chemicals (including petroleum products) (SU 3: Industrial use)
SU 9, Manufacture of fine chemicals (SU 3: Industrial use)
SU 17, General manufacturing, e.g. machinery, equipment, vehicles, other transport equipment. (SU 3: Industrial use)
SU 20, Health services (SU 3: Industrial use)
SU 0, Other (SU 3: Industrial use)

Environment contributing scenario(s):	
Industrial use of processing aids in processes and products, not becoming part of articles	ERC 4
Industrial use resulting in manufacture of another substance (use of intermediates)	ERC 6a
Industrial use of reactive processing aids	ERC 6b
Industrial use of sub-stances in closed systems	ERC 7
Worker contributing scenario(s):	
Use in closed process, no likelihood of exposure [Condition 1]	PROC 1
Use in closed process, no likelihood of exposure [Condition 2]	PROC 1
Use in closed, continuous process with occasional controlled exposure	PROC 2
Use in closed batch process (synthesis or formulation) [Condition 1]	PROC 3
Use in closed batch process (synthesis or formulation) [Condition 2]	PROC 3
Use in closed batch process (synthesis or formulation) [Condition 3]	PROC 3
Use in closed batch process (synthesis or formulation) [Condition 4]	PROC 3
Use in closed batch process (synthesis or formulation) [Condition 5]	PROC 3
Use in batch and other process (synthesis) where opportunity for exposure arises	PROC 4
Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)	PROC 5
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 1]	PROC 8a
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 2]	PROC 8a
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 1]	PROC 8b
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 2]	PROC 8b
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 3]	PROC 8b
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 4]	PROC 8b
Transfer of substance or preparation into small containers (dedicated filling line, including weighing)	PROC 9
Use as laboratory reagent	PROC 15
Hand-mixing with intimate contact and only PPE available	*PROC 19**

*PROC 19 is included in the uses advised against.

9.4.1. Environmental contributing scenario 1: Industrial use of processing aids in processes and products, not becoming part of articles

9.4.1.1. Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily use at site: **Confidential information**
• Annual use at a site: **Confidential information**
• Percentage of tonnage used at regional scale: **Confidential information**
Conditions and measures related to sewage treatment plant
• Municipal STP: Yes [Effectiveness Water: 87.37 %]
• Discharge rate of STP: ≥ 2E3 m^3/d
• Application of the STP sludge on agricultural soil: No
Conditions and measures related to treatment of waste (including article waste)
• Particular considerations on the waste treatment operations: No (low risk) (ERC based assessment demonstrating control of risk with default conditions. Low risk assumed for waste life stage. Waste disposal according to national/local legislation is sufficient.)
Other conditions affecting environmental exposure
• Receiving surface water flow rate: ≥ 1.8E4 m^3/d

9.4.1.2. Releases

With regard to the market data, different Environmental Release Categories were declared as relevant to this Exposure Scenario. The Use Descriptors ERC4, ERC 6a, ERC 6b and ERC 7 were provided by different Downstream Users to account for this Identified Use. In order to assess all of these Categories, the most critical release factor for each environmental compartment was assumed. In this case, the release factors of ERC 4 were applied. However, the release factor to water was modified and amounts to 10 %. This release factor is still more critical than the release factors to water defined by ERC 6a, ERC 6b and ERC 7.

The local releases to the environment are reported in the following table.

Table 150. Local releases to the environment

Release	Release factor estimation method	Explanation / Justification
Water	Release factor (Release factor to water (pharmaceutical application))	**Initial release factor:** 10% **Final release factor:** 10% **Local release rate:** **Confidential information** **Explanation / Justification:** The initial release factor to water was set to 10 % as worst case assumption. The release factor of 100 % as given by ERC 4 is highly overestimated. With regard to market data, most of the relevant Downstream Users declared that emissions to a sewage treatment plant do not occur. As a consequence, a release factor of 10 % was assumed which still represents a worst-case assumption.

Release	Release factor estimation method	Explanation / Justification
Air	ERC based	**Initial release factor:** 100% **Final release factor:** 100% **Local release rate:** **Confidential information**
Soil	ERC based	**Final release factor:** 5%

Releases to waste

Release factor to waste from the process: 0 %

No initial release to waste is given.

Further clarification for release factors (water, air)

The specific release factor for water of this Exposure Scenario is based on the Operational Conditions (OCs) described by different Downstream Users. The majority of the Downstream Users relevant to this Exposure Scenario declared that there is no substance release to a sewage treatment plant. In addition, Downstream Users who describe a substance release to wastewater reported only releases of trace amounts. As a consequence, the release factor for water of 100 % as defined by the conservative ERC (ERC 4) is highly overestimated. The assumed release factor of 10 % is much more reliable and still represents a worst-case assumption.

Risk Management Measures

On-site technology for air emission reduction is recommended but not obligatory to achieve an emission reduction. The default release factor to air amounts to 100 % as described by ERC 4.
Wastewater (if produced) is treated by on-site and/or off-site STP which ensures a typical removal efficiency of at least 87 % as predicted by the simple treat model (Technical Guidance Document on Risk Assessment, Part II, 2003) and by CHESAR (v2.2). The wastewater treatment techniques are based on separation techniques (sedimentation, oil-water separation) and biological treatment techniques (aerobic/anaerobic digestion processes, nitrification/denitrification).

9.4.1.3. Exposure and risks for the environment and man via the environment

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 151. Exposure concentrations and risks for the environment

Protection target	Exposure concentration	Risk characterisation
Freshwater	**Local PEC:** 1.457 mg/L	RCR = 0.049
Sediment (freshwater)	**Local PEC:** 5.594 mg/kg dw	RCR = 0.049
Marine water	**Local PEC:** 0.146 mg/L	RCR = 0.049
Sediment (marine water)	**Local PEC:** 0.559 mg/kg dw	RCR = 0.049
Sewage treatment plant	**Local PEC:** 14.52 mg/L	RCR = 0.118
Agricultural soil	**Local PEC:** 0.061 mg/kg dw	RCR < 0.01
Man via Environment - Inhalation	**Local PEC:** 0.518 mg/m³	RCR = 0.035
Man via Environment - Oral	**Exposure via food consumption:** 0.147 mg/kg bw/day	RCR = 0.368
Man via environment - combined routes		RCR = 0.402

Table 152. Contribution to oral intake for man via the environment from local contribution

Type of food	Estimated daily dose	Concentration in food
Drinking water	0.034 mg/kg bw/day	1.181 mg/L
Fish	0.002 mg/kg bw/day	1.417 mg/kg ww
Leaf crops	0.109 mg/kg bw/day	6.372 mg/kg ww
Root crops	0.002 mg/kg bw/day	0.312 mg/kg ww
Meat	1.909E-6 mg/kg bw/day	4.44E-4 mg/kg ww
Milk	3.558E-5 mg/kg bw/day	0.004 mg/kg ww

Conclusion on risk characterisation

The results of the calculation with the given data show, that the industrial use of the substance with the corresponding ERC (including a sector specific release factor) can be considered to be of acceptable risk for the environment, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.2. Worker contributing scenario 1: Use in closed process, no likelihood of exposure [Condition 1] (PROC 1)

9.4.2.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed system (minimal contact during routine operations)	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.4.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 153. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.007 mg/kg bw/day** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.002 mg/cm²** (TRA Worker v3)	RCR < 0.01
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.011
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.3. Worker contributing scenario 2: Use in closed process, no likelihood of exposure [Condition 2] (PROC 1)

9.4.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour*	TRA Worker v3

	Method
pressure extrapolation.	
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed system (minimal contact during routine operations)	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 100 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.4.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 154. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.007 mg/kg bw/day** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.002 mg/cm²** (TRA Worker v3)	RCR < 0.01
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.011
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.4. Worker contributing scenario 3: Use in closed, continuous process with occasional controlled exposure (PROC 2)

9.4.4.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Good general ventilation (3-5 air changes per hour)	TRA Worker v3
• Containment: Closed continuous process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.4.4.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 155. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**2.132 mg/m³** (TRA Worker v3)	RCR = 0.142
Inhalation, systemic, acute	**8.528 mg/m³** (TRA Worker v3)	RCR = 0.284
Inhalation, local, long-term	**2.132 mg/m³** (TRA Worker v3)	RCR = 0.142
Inhalation, local, acute	**8.528 mg/m³** (TRA Worker v3)	RCR = 0.284
Dermal, systemic, long-term	**0.274 mg/kg bw/day** (TRA Worker v3)	RCR = 0.347
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.04 mg/cm²** (TRA Worker v3)	RCR = 0.15

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.489
Combined routes, systemic, acute		RCR = 0.284 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.5. Worker contributing scenario 4: Use in closed batch process (synthesis or formulation) [Condition 1] (PROC 3)

9.4.5.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.4.5.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 156. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.457 mg/m³** (TRA Worker v3)	RCR = 0.03
Inhalation, systemic, acute	**1.827 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, local, long-term	**0.457 mg/m³** (TRA Worker v3)	RCR = 0.03
Inhalation, local, acute	**1.827 mg/m³** (TRA Worker v3)	RCR = 0.061
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Worker v3)	RCR = 0.044
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.038
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.074
Combined routes, systemic, acute		RCR = 0.061 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.6. Worker contributing scenario 5: Use in closed batch process (synthesis or formulation) [Condition 2] (PROC 3)

9.4.6.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 2.532E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3

	Method
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 50 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.4.6.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 157. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, systemic, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Worker v3)	RCR = 0.044
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.038
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.145
Combined routes, systemic, acute		RCR = 0.203 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.7. Worker contributing scenario 6: Use in closed batch process (synthesis or

formulation) [Condition 3] (PROC 3)

9.4.7.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 120 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.4.7.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 158. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Worker v3)	RCR = 0.044
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.038
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.145
Combined routes, systemic, acute		RCR = 0.203 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.8. Worker contributing scenario 7: Use in closed batch process (synthesis or formulation) [Condition 4] (PROC 3)

9.4.8.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	

	Method
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Worker v3
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 100 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.4.8.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 159. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**2.284 mg/m³** (TRA Worker v3)	RCR = 0.152
Inhalation, systemic, acute	**9.137 mg/m³** (TRA Worker v3)	RCR = 0.305
Inhalation, local, long-term	**2.284 mg/m³** (TRA Worker v3)	RCR = 0.152
Inhalation, local, acute	**9.137 mg/m³** (TRA Worker v3)	RCR = 0.305
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Worker v3)	RCR = 0.044
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.038
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.196
Combined routes, systemic, acute		RCR = 0.305 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding

PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.9. Worker contributing scenario 8: Use in closed batch process (synthesis or formulation) [Condition 5] (PROC 3)

9.4.9.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Outdoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.4.9.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 160. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.32 mg/m³** (TRA Worker v3)	RCR = 0.021
Inhalation, systemic, acute	**1.279 mg/m³** (TRA Worker v3)	RCR = 0.043
Inhalation, local, long-term	**0.32 mg/m³** (TRA Worker v3)	RCR = 0.021
Inhalation, local, acute	**1.279 mg/m³** (TRA Worker v3)	RCR = 0.043
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Worker v3)	RCR = 0.044
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.038
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic,		RCR = 0.065

Route of exposure and type of effects	Exposure concentration	Risk characterisation
long-term		
Combined routes, systemic, acute		RCR = 0.043 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.10. Worker contributing scenario 9: Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4)

9.4.10.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with basic employee training) [Effectiveness Dermal: 90 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.4.10.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 161. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.023 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.091 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.023 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.091 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Worker v3)	RCR = 0.868
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.1 mg/cm²** (TRA Worker v3)	RCR = 0.375
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.87
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.11. Worker contributing scenario 10: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) (PROC 5)

9.4.11.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not*	TRA Worker v3

	Method
need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.	
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
• Fume extraction hood: yes [Effectiveness Inhal: 98 %]	Manual calculation
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 100 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.4.11.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 162. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**45.68 mg/m³** (TRA Worker v3) Manual modification: **45.68 mg/m³ x 0.02 = 0.91 mg/m³**	RCR = 0.06
Inhalation, systemic, acute	**304.6 mg/m³** (TRA Worker v3) Manual modification: **304.6 mg/m³ x 0.02 = 6.10 mg/m³**	RCR = 0.203
Inhalation, local, long-term	**45.68 mg/m³** (TRA Worker v3) Manual modification: **45.68 mg/m³ x 0.02 = 0.91 mg/m³**	RCR = 0.06
Inhalation, local, acute	**304.6 mg/m³** (TRA Worker v3) Manual modification:	RCR = 0.203

Route of exposure and type of effects	Exposure concentration	Risk characterisation
	304.6 mg/m³ x 0.02 = 6.10 mg/m³	
Dermal, systemic, long-term	**0.411 mg/kg bw/day** (TRA Worker v3)	RCR = 0.521
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.06 mg/cm²** (TRA Worker v3)	RCR = 0.225
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.581
Combined routes, systemic, acute		RCR = 0.327 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

Additional Risk Management Measures need to be considered for this process since extraction fume hoods are applied. However, inhalation reduction based on this fume hood cannot be adequately implemented in the modelling tool. According to specific information given by relevant Downstream Users, the efficacy of the extraction hood refers to at least 20 air changes per hour. As a consequence, an additional inhalation exposure reduction of 98 % (reduction factor of 0.02) is manually applied.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.12. Worker contributing scenario 11: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 1] (PROC 8a)

9.4.12.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Good general ventilation (3-5 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	

	Method
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.4.12.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 163. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.107 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.426 mg/m³** (TRA Worker v3)	RCR = 0.014
Inhalation, local, long-term	**0.107 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.426 mg/m³** (TRA Worker v3)	RCR = 0.014
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Worker v3)	RCR = 0.868
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.875
Combined routes, systemic, acute		RCR = 0.014 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.13. Worker contributing scenario 12: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 2] (PROC 8a)

9.4.13.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25%	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 160 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.4.13.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 164. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**2.284 mg/m³** (TRA Workers 3.0)	RCR = 0.152
Inhalation, systemic, acute	**9.137 mg/m³** (TRA Workers 3.0)	RCR = 0.305
Inhalation, local, long-term	**2.284 mg/m³** (TRA Workers 3.0)	RCR = 0.152

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, local, acute	**9.137 mg/m³** (TRA Workers 3.0)	RCR = 0.305
Dermal, systemic, long-term	**0.411 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.521
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.03 mg/cm²** (TRA Workers 3.0)	RCR = 0.112
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.673
Combined routes, systemic, acute		RCR = 0.305 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.14. Worker contributing scenario 13: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 1] (PROC 8b)

9.4.14.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 95 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3

	Method
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.4.14.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 165. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.457 mg/m³** (TRA Worker v3)	RCR = 0.03
Inhalation, systemic, acute	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, long-term	**0.457 mg/m³** (TRA Worker v3)	RCR = 0.03
Inhalation, local, acute	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.102
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Worker v3)	RCR = 0.868
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.898
Combined routes, systemic, acute		RCR = 0.102 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.15. Worker contributing scenario 14: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 2] (PROC 8b)

9.4.15.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3

	Method
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 95 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific employee training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.4.15.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 166. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.023 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.152 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.023 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.152 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.868
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Workers 3.0)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.869
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be

worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.16. Worker contributing scenario 15: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 3] (PROC 8b)

9.4.16.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25%	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 95 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.4.16.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 167. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.082 mg/m³** (TRA Workers 3.0)	RCR < 0.01
Inhalation, systemic, acute	**0.548 mg/m³** (TRA Workers 3.0)	RCR = 0.018
Inhalation, local, long-term	**0.082 mg/m³** (TRA Workers 3.0)	RCR < 0.01
Inhalation, local, acute	**0.548 mg/m³** (TRA Workers 3.0)	RCR = 0.018

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Dermal, systemic, long-term	**0.411 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.521
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.03 mg/cm²** (TRA Workers 3.0)	RCR = 0.112
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.526
Combined routes, systemic, acute		RCR = 0.018 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.17. Worker contributing scenario 16: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [Condition 4] (PROC 8b)

9.4.17.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 1-5 %	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3

	Method
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.4.17.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 168. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.548 mg/m³** (TRA Worker v3)	RCR = 0.037
Inhalation, systemic, acute	**3.655 mg/m³** (TRA Worker v3)	RCR = 0.122
Inhalation, local, long-term	**0.548 mg/m³** (TRA Worker v3)	RCR = 0.037
Inhalation, local, acute	**3.655 mg/m³** (TRA Worker v3)	RCR = 0.122
Dermal, systemic, long-term	**0.548 mg/kg bw/day** (TRA Worker v3)	RCR = 0.694
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.04 mg/cm²** (TRA Worker v3)	RCR = 0.15
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.731
Combined routes, systemic, acute		RCR = 0.122 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.18. Worker contributing scenario 17: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) (PROC 9)

9.4.18.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3

	Method
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.4.18.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 169. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.046 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.01
Inhalation, local, long-term	**0.046 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.01
Dermal, systemic, long-term	**0.343 mg/kg bw/day** (TRA Worker v3)	RCR = 0.434
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.437
Combined routes, systemic, acute		RCR = 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management

Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.19. Worker contributing scenario 18: Use as laboratory reagent (PROC 15)

9.4.19.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.4.19.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 170. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, systemic, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Dermal, systemic, long-term	**0.068 mg/kg bw/day** (TRA Worker v3)	RCR = 0.086
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.02 mg/cm²** (TRA Worker v3)	RCR = 0.074
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Combined routes, systemic, long-term		RCR = 0.188
Combined routes, systemic, acute		RCR = 0.203 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.4.20. Worker contributing scenario 19: Hand-mixing with intimate contact and only PPE available (PROC 19)

9.4.20.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands and forearms (1980 cm^2)	TRA Worker v3

9.4.20.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 171. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.183 mg/m³** (TRA Worker v3)	RCR = 0.012
Inhalation, systemic, acute	**1.218 mg/m³** (TRA Worker v3)	RCR = 0.041
Inhalation, local, long-term	**0.183 mg/m³** (TRA Worker v3)	RCR = 0.012
Inhalation, local, acute	**1.218 mg/m³** (TRA Worker v3)	RCR = 0.041
Dermal, systemic, long-term	**7.072 mg/kg bw/day** (TRA Worker v3)	RCR = 8.951 >>>**CAUTION:** Risk not controlled <<<
Dermal, systemic, acute		>>>**CAUTION:** Risk not controlled <<<
Dermal, local, long-term	**0.25 mg/cm²** (TRA Worker v3)	RCR = 0.936
Dermal, local, acute		Covered by long-term effects (dermal, local, long-term)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 8.963
Combined routes, systemic, acute		RCR = 0.041 (only based on acute inhalation)

Conclusion on risk characterisation

Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC is unsafe. Even with specified Risk Management Measures (dermal protection with effectiveness of 95 %) unsafe use is demonstrated.
In conclusion, PROC 19 is included in the uses advised against.

9.5. Exposure scenario 5: Use at industrial site - Industrial use for the production of polymers

Sector of use:
SU 10, Formulation [mixing] of preparations and/or re-packaging (excluding alloys) (SU 3: Industrial use)
SU 12, Manufacture of plastics products, including compounding and conversion (SU 3: Industrial use)
SU 0, Other (SU 3: Industrial use)

Environment contributing scenario(s):	
Industrial use of processing aids in processes and products, not becoming part of articles	ERC 4
Industrial use resulting in manufacture of another substance (use of intermediates)	ERC 6a
Industrial use of monomers for manufacture of thermoplastics	ERC 6c
Industrial use of process regulators for polymerisation processes in production of resins, rubbers, polymers	ERC 6d
Industrial use of sub-stances in closed systems	ERC 7
Worker contributing scenario(s):	
Use in closed process, no likelihood of exposure [Condition 1]	PROC 1
Use in closed process, no likelihood of exposure [Condition 2]	PROC 1
Use in closed, continuous process with occasional controlled exposure [Condition 1]	PROC 2
Use in closed, continuous process with occasional controlled exposure [Condition 2]	PROC 2
Use in closed, continuous process with occasional controlled exposure [Condition 3]	PROC 2
Use in closed batch process (synthesis or formulation) [Condition 1]	PROC 3
Use in closed batch process (synthesis or formulation) [Condition 2]	PROC 3
Use in closed batch process (synthesis or formulation) [Condition 3]	PROC 3
Use in closed batch process (synthesis or formulation) [Condition 4]	PROC 3
Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 1]	PROC 4
Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 2]	PROC 4
Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 3]	PROC 4
Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 4]	PROC 4
Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 5]	PROC 4
Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 6]	PROC 4
Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)	PROC 5
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 1]	PROC 8a

Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 2]	PROC 8a
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities	PROC 8b
Transfer of substance or preparation into small containers (dedicated filling line, including weighing)	PROC 9
Roller application or brushing	*PROC 10**
Use as laboratory reagent	PROC 15

*PROC 10 is included in the uses advised against.

9.5.1. Environmental contributing scenario 1: Industrial use of processing aids in processes and products, not becoming part of articles

9.5.1.1. Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily use at site: **Confidential information**
• Annual use at a site: **Confidential information**
• Percentage of tonnage used at regional scale: **Confidential information**
Conditions and measures related to sewage treatment plant
• Municipal STP: Yes [Effectiveness Water: 100 %]
• Discharge rate of STP: ≥ 2E3 m^3/d
• Application of the STP sludge on agricultural soil: No
Conditions and measures related to treatment of waste (including article waste)
• Particular considerations on the waste treatment operations: No (low risk) (ERC based assessment demonstrating control of risk with default conditions. Low risk assumed for waste life stage. Waste disposal according to national/local legislation is sufficient.)
Other conditions affecting environmental exposure
• Receiving surface water flow rate: ≥ 1.8E4 m^3/d

9.5.1.2. Releases

With regard to the market data, different Environmental Release Categories were declared as relevant to this Exposure Scenario. The Use Descriptors ERC4, ERC 6a, ERC 6c, ERC 6d and ERC 7 were provided by different Downstream Users to account for this Identified Use. In order to assess all of these Categories, the most critical release factor for each environmental compartment was assumed. With regard to environmental release to water, the release factor was modified by taking reliable market data and relevant OCs and RMMs into account. According to market data, most of the relevant Downstream Users declared that emissions to a sewage treatment plant do not occur.

The local releases to the environment are reported in the following table.

Table 172. Local releases to the environment

Release	Release factor estimation method	Explanation / Justification
Water	Release factor (Release factor to water	**Initial release factor:** 1% **Final release factor:** 1% **Local release rate:** **Confidential information**

Release	Release factor estimation method	Explanation / Justification
	(polymer production))	**Explanation / Justification:** Environmental release to water is most critical as defined by ERC 4 (100%). The relevant release factor to water given by ERC 6c and ERC 7 amounts to 5%, respectively. However, these release factors are considered as highly overestimated. This is based on the available market data and the applied Operational Conditions (OCs) and the Risk Management Measures (RMMs) relevant to this Identified Use.
Air	Release factor (ERC 6d (default release to air))	**Initial release factor:** 35% **Final release factor:** 35% **Local release rate:** **Confidential information** **Explanation / Justification:** Environmental release to air is most critical as defined by ERC 4 (100%). However, this release factor is considered as highly overestimated due to the given Operational Conditions (OCs) and Risk Management Measures (RMMs). As a consequence, the release factor to air as defined by ERC 6d (35%) was applied.
Soil	Release factor (ERC 7 (default release to soil))	**Final release factor:** 5% **Explanation / Justification:** With regard to environmental releases to soil, ERC 4 and ERC 7 describe the most critical release (5%).

Further clarification for release factors (water, air)

The estimated release factors for this Exposure Scenario are based on the Operational Conditions (OCs) and the Risk Management Measures (RMMs) as listed below.

Operational Conditions

The process is optimized for highly efficient use of raw material which leads to a very minimal environmental release. The processes are performed without water contact. Wastewater emissions are only generated from equipment cleaning with water.

Risk Management Measures

On-site technology for air emission reduction takes place for indoor applications. Appropriate air removal techniques to achieve the required emission reduction are listed below.

- Wet scrubber (gas removal): typical efficiency of 70 %
- Thermal oxidation: typical efficiency of 98 %
- Vapour recovery (adsorption): typical efficiency of 80 %

Wastewater (if produced) is treated by on-site and/or off-site STP which ensures a typical removal efficiency of at least 87 % as predicted by the simple treat model (Technical Guidance Document on Risk Assessment, Part II, 2003) and by CHESAR (v2.2). The wastewater treatment techniques are based on separation techniques (sedimentation, oil-water separation) and biological treatment techniques (aerobic/anaerobic digestion processes, nitrification/denitrification).

Releases to waste

Release factor to waste from the process: 0 %

No initial release to waste is given.

9.5.1.3. Exposure and risks for the environment and man via the environment

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 173. Exposure concentrations and risks for the environment

Protection target	Exposure concentration	Risk characterisation
Freshwater	**Local PEC:** 2.152 mg/L	RCR = 0.072
Sediment (freshwater)	**Local PEC:** 8.262 mg/kg dw	RCR = 0.072
Marine water	**Local PEC:** 0.215 mg/L	RCR = 0.072
Sediment (marine water)	**Local PEC:** 0.826 mg/kg dw	RCR = 0.072
Sewage treatment plant	**Local PEC:** 21.47 mg/L	RCR = 0.175
Agricultural soil	**Local PEC:** 0.105 mg/kg dw	RCR < 0.01
Man via Environment - Inhalation	**Local PEC:** 0.906 mg/m³	RCR = 0.06
Man via Environment - Oral	**Exposure via food consumption:** 0.212 mg/kg bw/day	RCR = 0.531
Man via environment - combined routes		RCR = 0.591

Table 174. Contribution to oral intake for man via the environment from local contribution

Type of food	Estimated daily dose	Concentration in food
Drinking water	0.017 mg/kg bw/day	0.593 mg/L
Fish	0.001 mg/kg bw/day	0.711 mg/kg ww
Leaf crops	0.191 mg/kg bw/day	11.15 mg/kg ww
Root crops	0.003 mg/kg bw/day	0.54 mg/kg ww
Meat	3.064E-6 mg/kg bw/day	7.125E-4 mg/kg ww
Milk	5.71E-5 mg/kg bw/day	0.007 mg/kg ww

Conclusion on risk characterisation

The results of the calculation with the given data show, that the industrial use of the substance with the relevant release factors can be considered to be of acceptable risk for the environment, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.2. Worker contributing scenario 1: Use in closed process, no likelihood of exposure [Condition 1] (PROC 1)

9.5.2.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	

	Method
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed system (minimal contact during routine operations)	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.5.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 175. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.007 mg/kg bw/day** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.002 mg/cm²** (TRA Worker v3)	RCR < 0.01
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.011
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management

Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.3. Worker contributing scenario 2: Use in closed process, no likelihood of exposure [Condition 2] (PROC 1)

9.5.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed system (minimal contact during routine operations)	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 100 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.5.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 176. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.007 mg/kg bw/day** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.002 mg/cm²** (TRA Worker v3)	RCR < 0.01
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.011
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.4. Worker contributing scenario 3: Use in closed, continuous process with occasional controlled exposure [Condition 1] (PROC 2)

9.5.4.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed continuous process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	

	Method
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.5.4.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 177. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.068 mg/kg bw/day** (TRA Worker v3)	RCR = 0.087
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.037
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.089
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.5. Worker contributing scenario 4: Use in closed, continuous process with occasional controlled exposure [Condition 2] (PROC 2)

9.5.5.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed continuous process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.5.5.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 178. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.02
Inhalation, systemic, acute	**1.218 mg/m³** (TRA Worker v3)	RCR = 0.041
Inhalation, local, long-term	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.02
Inhalation, local, acute	**1.218 mg/m³** (TRA Worker v3)	RCR = 0.041
Dermal, systemic, long-term	**0.274 mg/kg bw/day** (TRA Worker v3)	RCR = 0.347
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.04 mg/cm²** (TRA Worker v3)	RCR = 0.15
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.367
Combined routes, systemic, acute		RCR = 0.041 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.6. Worker contributing scenario 5: Use in closed, continuous process with occasional controlled exposure [Condition 3] (PROC 2)

9.5.6.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25 %	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Worker v3
• Containment: Closed continuous process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 90 °C	TRA Worker v3

	Method
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.5.6.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 179. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.371 mg/m³** (TRA Worker v3)	RCR = 0.091
Inhalation, systemic, acute	**5.482 mg/m³** (TRA Worker v3)	RCR = 0.183
Inhalation, local, long-term	**1.371 mg/m³** (TRA Worker v3)	RCR = 0.091
Inhalation, local, acute	**5.482 mg/m³** (TRA Worker v3)	RCR = 0.183
Dermal, systemic, long-term	**0.164 mg/kg bw/day** (TRA Worker v3)	RCR = 0.208
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.024 mg/cm²** (TRA Worker v3)	RCR = 0.09
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.3
Combined routes, systemic, acute		RCR = 0.183 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.7. Worker contributing scenario 6: Use in closed batch process (synthesis or formulation) [Condition 1] (PROC 3)

9.5.7.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	

	Method
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.5.7.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 180. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, systemic, acute	**3.655 mg/m³** (TRA Worker v3)	RCR = 0.122
Inhalation, local, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, local, acute	**3.655 mg/m³** (TRA Worker v3)	RCR = 0.122
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Worker v3)	RCR = 0.044
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.038
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.105
Combined routes, systemic, acute		RCR = 0.122 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at

least equivalent levels.

9.5.8. Worker contributing scenario 7: Use in closed batch process (synthesis or formulation) [Condition 2] (PROC 3)

9.5.8.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with basic employee training) [Effectiveness Dermal: 90 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 80 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.5.8.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 181. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.761 mg/m³** (TRA Worker v3)	RCR = 0.051
Inhalation, systemic, acute	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, long-term	**0.761 mg/m³** (TRA Worker v3)	RCR = 0.051
Inhalation, local, acute	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.102
Dermal, systemic, long-term	**0.069 mg/kg bw/day** (TRA Worker v3)	RCR = 0.087
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.02 mg/cm²** (TRA Worker v3)	RCR = 0.075
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.138
Combined routes, systemic, acute		RCR = 0.102 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.9. Worker contributing scenario 8: Use in closed batch process (synthesis or formulation) [Condition 3] (PROC 3)

9.5.9.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	TRA Worker v3
• Vapour pressure at elevated temperature: < 7.491E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Worker v3
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3

	Method
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 70 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.5.9.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 182. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, systemic, acute	**3.655 mg/m³** (TRA Worker v3)	RCR = 0.122
Inhalation, local, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, local, acute	**3.655 mg/m³** (TRA Worker v3)	RCR = 0.122
Dermal, systemic, long-term	**0.138 mg/kg bw/day** (TRA Worker v3)	RCR = 0.175
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.04 mg/cm²** (TRA Worker v3)	RCR = 0.151
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.236
Combined routes, systemic, acute		RCR = 0.122 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.10. Worker contributing scenario 9: Use in closed batch process (synthesis or

formulation) [Condition 4] (PROC 3)

9.5.10.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 7.491E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Good general ventilation (3-5 air changes per hour)	TRA Worker v3
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0%]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80%]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90%]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 70 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.5.10.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 183. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**2.132 mg/m³** (TRA Worker v3)	RCR = 0.142
Inhalation, systemic, acute	**8.528 mg/m³** (TRA Worker v3)	RCR = 0.284
Inhalation, local, long-term	**2.132 mg/m³** (TRA Worker v3)	RCR = 0.142
Inhalation, local, acute	**8.528 mg/m³** (TRA Worker v3)	RCR = 0.284
Dermal, systemic, long-term	**0.138 mg/kg bw/day** (TRA Worker v3)	RCR = 0.175
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.04 mg/cm²** (TRA Worker v3)	RCR = 0.151
Dermal, local, acute		Qualitative (see below)

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.317
Combined routes, systemic, acute		RCR = 0.284

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.11. Worker contributing scenario 9: Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 1] (PROC 4)

9.5.11.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3

	Method
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95%]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 140 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.5.11.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 184. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, systemic, acute	**3.655 mg/m³** (TRA Worker v3)	RCR = 0.122
Inhalation, local, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, local, acute	**3.655 mg/m³** (TRA Worker v3)	RCR = 0.122
Dermal, systemic, long-term	**0.343 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.434
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Workers 3.0)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.495
Combined routes, systemic, acute		RCR = 0.122 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.12. Worker contributing scenario 10: Use in batch and other process (synthesis)

where opportunity for exposure arises [Condition 2] (PROC 4)

9.5.12.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	TRA Worker v3
• Vapour pressure at elevated temperature: < 3.362E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 55 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.5.12.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 185. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.02
Inhalation, systemic, acute	**1.218 mg/m³** (TRA Worker v3)	RCR = 0.041
Inhalation, local, long-term	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.02
Inhalation, local, acute	**1.218 mg/m³** (TRA Worker v3)	RCR = 0.041
Dermal, systemic, long-term	**0.343 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.434
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Workers 3.0)	RCR = 0.187

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.454
Combined routes, systemic, acute		RCR = 0.041 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.13. Worker contributing scenario 11: Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 3] (PROC 4)

9.5.13.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: < 1 %	TRA Worker v3
• Vapour pressure at elevated temperature: < 2.532E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3

	Method
• Process temperature (for liquid): ≤ 50 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.5.13.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 186. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.609 mg/m³** (TRA Worker v3)	RCR = 0.041
Inhalation, systemic, acute	**2.436 mg/m³** (TRA Worker v3)	RCR = 0.081
Inhalation, local, long-term	**0.609 mg/m³** (TRA Worker v3)	RCR = 0.041
Inhalation, local, acute	**2.436 mg/m³** (TRA Worker v3)	RCR = 0.081
Dermal, systemic, long-term	**0.137 mg/kg bw/day** (TRA Worker v3)	RCR = 0.174
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.02 mg/cm²** (TRA Worker v3)	RCR = 0.075
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.214
Combined routes, systemic, acute		RCR = 0.081 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.14. Worker contributing scenario 12: Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 4] (PROC 4)

9.5.14.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3

	Method
Technical and organisational conditions and measures	
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with basic employee training) [Effectiveness Dermal: 90 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Outdoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.5.14.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 187. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.32 mg/m³** (TRA Worker v3)	RCR = 0.021
Inhalation, systemic, acute	**2.132 mg/m³** (TRA Worker v3)	RCR = 0.071
Inhalation, local, long-term	**0.32 mg/m³** (TRA Worker v3)	RCR = 0.021
Inhalation, local, acute	**2.132 mg/m³** (TRA Worker v3)	RCR = 0.071
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Worker v3)	RCR = 0.868
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.1 mg/cm²** (TRA Worker v3)	RCR = 0.375
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.89
Combined routes, systemic, acute		RCR = 0.071 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.15. Worker contributing scenario 13: Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 5] (PROC 4)

9.5.15.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25 %	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with basic employee training) [Effectiveness Dermal: 90%]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.5.15.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 188. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, systemic, acute	**3.655 mg/m³** (TRA Worker v3)	RCR = 0.122
Inhalation, local, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, local, acute	**3.655 mg/m³** (TRA Worker v3)	RCR = 0.122
Dermal, systemic, long-term	**0.412 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.521
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.06 mg/cm²** (TRA Workers 3.0)	RCR = 0.225
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.582

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Combined routes, systemic, acute		RCR = 0.122 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.16. Worker contributing scenario 14: Use in batch and other process (synthesis) where opportunity for exposure arises [Condition 6] (PROC 4)

9.5.16.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with basic employee training) [Effectiveness Dermal: 90%]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.5.16.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 189. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.046 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.183 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.046 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.183 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.868
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.1 mg/cm²** (TRA Workers 3.0)	RCR = 0.375
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.871
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.17. Worker contributing scenario 15: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) (PROC 5)

9.5.17.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25%	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374	TRA Worker v3

	Method
with specific activity training) [Effectiveness Dermal: 95 %]	
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.5.17.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 190. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.457 mg/m³** (TRA Workers 3.0)	RCR = 0.03
Inhalation, systemic, acute	**1.827 mg/m³** (TRA Workers 3.0)	RCR = 0.061
Inhalation, local, long-term	**0.457 mg/m³** (TRA Workers 3.0)	RCR = 0.03
Inhalation, local, acute	**1.827 mg/m³** (TRA Workers 3.0)	RCR = 0.061
Dermal, systemic, long-term	**0.411 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.521
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.06 mg/cm²** (TRA Workers 3.0)	RCR = 0.225
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.551
Combined routes, systemic, acute		RCR = 0.061 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.18. Worker contributing scenario 16: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 1] (PROC 8a)

9.5.18.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.5.18.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 191. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.02
Inhalation, systemic, acute	**1.218 mg/m³** (TRA Worker v3)	RCR = 0.041
Inhalation, local, long-term	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.02
Inhalation, local, acute	**1.218 mg/m³** (TRA Worker v3)	RCR = 0.041
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Worker v3)	RCR = 0.868
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.888
Combined routes, systemic, acute		RCR = 0.041 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.19. Worker contributing scenario 17: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities [Condition 2] (PROC 8a)

9.5.19.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Good general ventilation (3-5 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with basic employee training) [Effectiveness Dermal: 90 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 80 °C	TRA Worker v3

	Method
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.5.19.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 192. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.066 mg/m³** (TRA Worker v3)	RCR = 0.071
Inhalation, systemic, acute	**21.32 mg/m³** (TRA Worker v3)	RCR = 0.711
Inhalation, local, long-term	**1.066 mg/m³** (TRA Worker v3)	RCR = 0.071
Inhalation, local, acute	**21.32 mg/m³** (TRA Worker v3)	RCR = 0.711
Dermal, systemic, long-term	**0.274 mg/kg bw/day** (TRA Worker v3)	RCR = 0.347
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.02 mg/cm²** (TRA Worker v3)	RCR = 0.075
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.418
Combined routes, systemic, acute		RCR = 0.711 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.20. Worker contributing scenario 18: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b)

9.5.20.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	

	Method
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 95 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95%]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.5.20.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 193. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.076 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.01
Inhalation, local, long-term	**0.076 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.01
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.868
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Workers 3.0)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.873
Combined routes, systemic, acute		RCR = 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management

Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.21. Worker contributing scenario 19: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) (PROC 9)

9.5.21.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	TRA Worker v3
• Vapour pressure at elevated temperature: < 4.427E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Good general ventilation (3-5 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with basic employee training) [Effectiveness Dermal: 90 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 60 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.5.21.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 194. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.64 mg/m³** (TRA Worker v3)	RCR = 0.043
Inhalation, systemic, acute	**4.264 mg/m³** (TRA Worker v3)	RCR = 0.142
Inhalation, local, long-term	**0.64 mg/m³** (TRA Worker v3)	RCR = 0.043
Inhalation, local, acute	**4.264 mg/m³** (TRA Worker v3)	RCR = 0.142

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Dermal, systemic, long-term	**0.412 mg/kg bw/day** (TRA Worker v3)	RCR = 0.521
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.06 mg/cm²** (TRA Worker v3)	RCR = 0.225
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.564
Combined routes, systemic, acute		RCR = 0.142 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.5.22. Worker contributing scenario 20: Roller application or brushing (PROC 10)

9.5.22.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3

	Method
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 130 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.5.22.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 195. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**4.568 mg/m³** (TRA Worker v3)	RCR = 0.305
Inhalation, systemic, acute	**30.46 mg/m³** (TRA Worker v3)	RCR = 1.015 >>>**CAUTION:** Risk not controlled <<<
Inhalation, local, long-term	**4.568 mg/m³** (TRA Worker v3)	RCR = 0.305
Inhalation, local, acute	**30.46 mg/m³** (TRA Worker v3)	RCR = 1.015 >>>**CAUTION:** Risk not controlled <<<
Dermal, systemic, long-term	**0.823 mg/kg bw/day** (TRA Worker v3)	RCR = 1.042 >>>**CAUTION:** Risk not controlled <<<
Dermal, systemic, acute		Covered by long-term effects (dermal, systemic, long-term)
Dermal, local, long-term	**0.06 mg/cm²** (TRA Worker v3)	RCR = 0.225
Dermal, local, acute		Covered by long-term effects (dermal, local, long-term)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 1.346 >>>**CAUTION:** Risk not controlled <<<
Combined routes, systemic,		RCR = 1.015 (only based on

Route of exposure and type of effects	Exposure concentration	Risk characterisation
acute		acute inhalation) >>>**CAUTION:** Risk <u>not</u> controlled <<<

<u>Conclusion on risk characterisation</u>

Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC bears a potential risk for workers. Despite a high level of respiratory protection, the RCRs for acute inhalation exceed the trigger value of 1. By implementing a more effective respiratory protection, safe use could be achieved. However, this is considered as not practicable. In addition, PROC 10 is generally associated with a high dermal and inhalation exposure which is based on the inherent nature of the PROC. As a consequence of these calculations/conclusions, PROC 10 is included in the uses advised against.

9.5.23. Worker contributing scenario 21: Use as laboratory reagent (PROC 15)

9.5.23.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.5.23.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 196. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.152 mg/m³** (TRA Worker v3)	RCR = 0.01
Inhalation, systemic, acute	**0.609 mg/m³** (TRA Worker v3)	RCR = 0.02
Inhalation, local, long-term	**0.152 mg/m³** (TRA Worker v3)	RCR = 0.01
Inhalation, local, acute	**0.609 mg/m³** (TRA Worker v3)	RCR = 0.02
Dermal, systemic, long-term	**0.068 mg/kg bw/day** (TRA Worker v3)	RCR = 0.086
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.02 mg/cm²** (TRA Worker v3)	RCR = 0.074
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.096
Combined routes, systemic, acute		RCR = 0.02 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.6. Exposure scenario 6: Use at industrial site - Industrial use for the production of textiles, leather and fur

Sector of use:
SU 5, Manufacture of textiles, leather, fur (SU 3: Industrial use)
SU 18, Manufacture of furniture (SU 3: Industrial use)
SU 0, Other (SU 3: Industrial use)

Environment contributing scenario(s):	
Industrial use of processing aids in processes and products, not becoming part of articles	ERC 4
Industrial use resulting in manufacture of another substance (use of intermediates)	ERC 6a
Industrial use of monomers for manufacture of thermoplastics	ERC 6c
Industrial use of process regulators for polymerisation processes in production of resins, rubbers, polymers	ERC 6d
Worker contributing scenario(s):	
Use in closed process, no likelihood of exposure	PROC 1
Use in closed, continuous process with occasional controlled exposure	PROC 2
Use in closed batch process (synthesis or formulation)	PROC 3
Use in batch and other process (synthesis) where opportunity for exposure arises	PROC 4
Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)	PROC 5
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities	PROC 8b
Transfer of substance or preparation into small containers (dedicated filling line, including weighing)	PROC 9

9.6.1. Environmental contributing scenario 1: Industrial use of processing aids in processes and products, not becoming part of articles

9.6.1.1. Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily use at site: **Confidential information**
• Annual use at a site: **Confidential information**
• Percentage of tonnage used at regional scale: **Confidential information**
Conditions and measures related to sewage treatment plant
• Municipal STP: Yes [Effectiveness Water: 87.37 %]
• Discharge rate of STP: ≥ 2E3 m^3/d
• Application of the STP sludge on agricultural soil: No
Conditions and measures related to treatment of waste (including article waste)
• Particular considerations on the waste treatment operations: No (low risk) (ERC based assessment demonstrating control of risk with default conditions. Low risk assumed for waste life stage. Waste disposal according to national/local legislation is sufficient.)
Other conditions affecting environmental exposure

• Receiving surface water flow rate: ≥ 1.8E4 m^3/d

9.6.1.2. Releases

With regard to the market data, different Environmental Release Categories were declared as relevant to this Exposure Scenario. The Use Descriptors ERC4, ERC 6a, ERC 6c and ERC 6d were provided by different Downstream Users to account for this Identified Use. In order to assess all of these Categories, the most critical release factor for each environmental compartment should actually be assumed. However, the release factor to water amounts to 3 %. Referring to reliable market data, the release of wastewater to a STP can be excluded. All Downstream Users relevant to this Identified Use declared that there are no releases to a STP. Consequently, the release factor of 3 % still represents a worst-case assumption and is, therefore, justified.

This release factor is still more critical than the release factors to water defined by ERC 6a, ERC 6c and ERC 6d.

The local releases to the environment are reported in the following table.

Table 197. Local releases to the environment

Release	Release factor estimation method	Explanation / Justification
Water	Release factor (Release factor to water (textile industry))	**Initial release factor:** 3% **Final release factor:** 3% **Local release rate:** **Confidential information** **Explanation / Justification:** According to the default release factor for ERC 4, 100 % of release to water should be assumed. However, this is considered as an overestimation. With regard to market data, emissions to waste water do not occur. All relevant Downstream Users state that no emission to a sewage treatment plant occurs. As a consequence, a release factor of 3 % was assumed which still represents a worst-case assumption.
Air	ERC based	**Initial release factor:** 100% **Final release factor:** 100% **Local release rate:** **Confidential information**
Soil	ERC based	**Final release factor:** 5%

Further clarification for release factors (water, air)

The specific release factor for water of this Exposure Scenario is based on the Operational Conditions (OCs) described by different Downstream Users. All Downstream Users relevant to this Exposure Scenario declared that there is no substance release to a sewage treatment plant. As a consequence, the release factor for water of 100 % as defined by the conservative ERC (ERC 4) is highly overestimated. The assumed release factor of 3 % is much more reliable and still represents a worst-case assumption.

Operational Conditions

The processes should exclude the substance release to a sewage treatment plant. This can be achieved by different distillation techniques used to treat wastewater. If wastewater is produced and discharged to a STP, the Risk Management Measures (RMMs) as listed below need to be implemented to ensure an appropriate substance removal.

Risk Management Measures

On-site technology for air emission reduction is recommended but not obligatory to achieve an emission reduction. The default release factor to air amounts to 100 % as described by ERC 4.

If wastewater is released to a STP, a typical substance removal efficiency of at least 87 % takes place as predicted by the simple treat model (Technical Guidance Document on Risk Assessment, Part II, 2003) and by CHESAR (v2.2). The wastewater treatment techniques are based on separation techniques (sedimentation, oil-water separation) and biological treatment techniques (aerobic/anaerobic digestion processes, nitrification/denitrification).

Releases to waste

Release factor to waste from the process: 0 %

No initial release to waste is given.

9.6.1.3. Exposure and risks for the environment and man via the environment

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 198. Exposure concentrations and risks for the environment

Protection target	Exposure concentration	Risk characterisation
Freshwater	**Local PEC:** 2.846 mg/L	RCR = 0.095
Sediment (freshwater)	**Local PEC:** 10.93 mg/kg dw	RCR = 0.095
Marine water	**Local PEC:** 0.285 mg/L	RCR = 0.095
Sediment (marine water)	**Local PEC:** 1.093 mg/kg dw	RCR = 0.095
Sewage treatment plant	**Local PEC:** 28.42 mg/L	RCR = 0.231
Agricultural soil	**Local PEC:** 0.132 mg/kg dw	RCR < 0.01
Man via Environment - Inhalation	**Local PEC:** 1.143 mg/m³	RCR = 0.076
Man via Environment - Oral	**Exposure via food consumption:** 0.269 mg/kg bw/day	RCR = 0.672
Man via environment - combined routes		RCR = 0.748

Table 199. Contribution to oral intake for man via the environment from local contribution

Type of food	Estimated daily dose	Concentration in food
Drinking water	0.022 mg/kg bw/day	0.783 mg/L
Fish	0.002 mg/kg bw/day	0.94 mg/kg ww
Leaf crops	0.241 mg/kg bw/day	14.05 mg/kg ww
Root crops	0.004 mg/kg bw/day	0.678 mg/kg ww
Meat	3.869E-6 mg/kg bw/day	8.997E-4 mg/kg ww
Milk	7.21E-5 mg/kg bw/day	0.009 mg/kg ww

Conclusion on risk characterisation

The results of the calculation with the given data show, that the industrial use of the substance with the corresponding ERC (including a sector specific release factor) can be considered to be of acceptable risk for the environment, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users

should ensure that risks are managed to at least equivalent levels.

9.6.2. Worker contributing scenario 1: Use in closed process, no likelihood of exposure (PROC 1)

9.6.2.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed system (minimal contact during routine operations)	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 100 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.6.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 200. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic,	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01

Route of exposure and type of effects	Exposure concentration	Risk characterisation
long-term		
Inhalation, systemic, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.007 mg/kg bw/day** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.002 mg/cm²** (TRA Worker v3)	RCR < 0.01
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.011
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.6.3. Worker contributing scenario 2: Use in closed, continuous process with occasional controlled exposure (PROC 2)

9.6.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 7.491E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed continuous process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3

	Method
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 70 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.6.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 201. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, systemic, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Dermal, systemic, long-term	**0.068 mg/kg bw/day** (TRA Worker v3)	RCR = 0.087
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.037
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.188
Combined routes, systemic, acute		RCR = 0.203 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.6.4. Worker contributing scenario 3: Use in closed batch process (synthesis or formulation) (PROC 3)

9.6.4.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 100 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.6.4.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 202. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, systemic, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, local, long-term	**1.523 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Worker v3)	RCR = 0.044
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.038
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.145
Combined routes, systemic, acute		RCR = 0.203 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.6.5. Worker contributing scenario 4: Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4)

9.6.5.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3

	Method
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.6.5.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 203. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.152 mg/m³** (TRA Worker v3)	RCR = 0.01
Inhalation, systemic, acute	**0.609 mg/m³** (TRA Worker v3)	RCR = 0.02
Inhalation, local, long-term	**0.152 mg/m³** (TRA Worker v3)	RCR = 0.01
Inhalation, local, acute	**0.609 mg/m³** (TRA Worker v3)	RCR = 0.02
Dermal, systemic, long-term	**0.343 mg/kg bw/day** (TRA Worker v3)	RCR = 0.434
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.444
Combined routes, systemic, acute		RCR = 0.02 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.6.6. Worker contributing scenario 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) (PROC 5)

9.6.6.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3

	Method
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.6.6.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 204. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.152 mg/m³** (TRA Worker v3)	RCR = 0.01
Inhalation, systemic, acute	**0.609 mg/m³** (TRA Worker v3)	RCR = 0.02
Inhalation, local, long-term	**0.152 mg/m³** (TRA Worker v3)	RCR = 0.01
Inhalation, local, acute	**0.609 mg/m³** (TRA Worker v3)	RCR = 0.02
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Worker v3)	RCR = 0.868
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.1 mg/cm²** (TRA Worker v3)	RCR = 0.374
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.878
Combined routes, systemic, acute		RCR = 0.02 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.6.7. Worker contributing scenario 6: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b)

9.6.7.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 95 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.6.7.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 205. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.076 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.01
Inhalation, local, long-term	**0.076 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.305 mg/m³** (TRA Worker v3)	RCR = 0.01
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Worker v3)	RCR = 0.868

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.873
Combined routes, systemic, acute		RCR = 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.6.8. Worker contributing scenario 7: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) (PROC 9)

9.6.8.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 7.491E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness	TRA Worker v3

	Method
Inhal: 90 %]	
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 70 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.6.8.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 206. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, systemic, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, long-term	**0.914 mg/m³** (TRA Worker v3)	RCR = 0.061
Inhalation, local, acute	**6.091 mg/m³** (TRA Worker v3)	RCR = 0.203
Dermal, systemic, long-term	**0.206 mg/kg bw/day** (TRA Worker v3)	RCR = 0.26
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.03 mg/cm²** (TRA Worker v3)	RCR = 0.112
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.321
Combined routes, systemic, acute		RCR = 0.203 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.7. Exposure scenario 7: Use at industrial site - Industrial use for the manufacture of non-metallic mineral products

Sector of use:
SU 13, Manufacture of other non-metallic mineral products, e.g. plasters, cement (SU 3: Industrial use)
SU 0, Other (SU 3: Industrial use)

Environment contributing scenario(s):	
Industrial use of processing aids in processes and products, not becoming part of articles	ERC 4
Worker contributing scenario(s):	
Use in closed process, no likelihood of exposure	PROC 1
Use in closed, continuous process with occasional controlled exposure	PROC 2
Use in closed batch process (synthesis or formulation)	PROC 3
Industrial spraying	PROC 7

Description of the technical process covered by the SpERC: ESVOC SpERC 4.3a.v1

Process Categories: 1 (use in closed process, no likelihood of exposure), 2 (use in closed, continuous process with occasional controlled exposure), 3 (use in closed batch process (synthesis or formulation)), 4 (use in batch and other process (synthesis) where opportunity for exposure arises), 5 (mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)), 7 (industrial spraying), 8a (transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities), 8b (transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities), 10 (roller application or brushing), 13 (treatment of articles by dipping and pouring), 15 (use as laboratory reagent)

9.7.1. Environmental contributing scenario 1: Industrial use of processing aids in processes and products, not becoming part of articles

9.7.1.1. Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily use at site: **Confidential information**
• Annual use at a site: **Confidential information**
• Percentage of tonnage used at regional scale: = **Confidential information**
Conditions and measures related to sewage treatment plant
• Municipal STP: Yes [Effectiveness Water: 87.37 %]
• Discharge rate of STP: ≥ 2E3 m^3/d
• Application of the STP sludge on agricultural soil: No
Conditions and measures related to treatment of waste (including article waste)
• Particular considerations on the waste treatment operations: No (low risk) (ERC based assessment demonstrating control of risk with default conditions. Low risk assumed for waste life stage. Waste disposal according to national/local legislation is sufficient.)
Other conditions affecting environmental exposure
• Receiving surface water flow rate: ≥ 1.8E4 m^3/d

9.7.1.2. Releases

The local releases to the environment are reported in the following table.

Table 207. Local releases to the environment

Release	Release factor estimation method	Explanation / Justification
Water	SpERC based ESVOC SpERC 4.3a.v1 - ESVOC SpERC 4.3a.v1 (1) Use in Coatings (industrial) - Use in Coatings	**Initial release factor:** 2 % **Final release factor:** 2 % **Local release rate:** **Confidential information** **Explanation / Justification:** Justification is provided by ESVOC SpERC fact sheet (Use in Coatings, V1) as follows: Emission factors to wastewater are conservatively calculated based on wastewater volume generated from blanket wash and cleaning of printing machines and substance aqueous solubility. Assumption of 20 m³ of wastewater generated per 1 tonne of substance used is relatively conservative. Example: 1 mg/L x 20 m³/tonne use x 1000 L/m³ x 1 tonne/10xE9 mg = 0.00002 tonnes/tonne used. For WS range (e.g., 1-10 mg/L), the geometric mean (i.e., 3.2 mg/L) is used to calculate the fraction released.
Air	SpERC based same as above	**Initial release factor:** 98 % **Final release factor:** 98 % **Local release rate:** **Confidential information** **Explanation / Justification:** Justification is provided by ESVOC SpERC fact sheet (Use in Coatings, V1) as follows: OECD Coatings ESD.
Soil	SpERC based same as above	**Final release factor:** 0 % **Explanation / Justification:** Justification is provided by ESVOC SpERC fact sheet (Use in Coatings, V1) as follows: OECD Coatings ESD.

Further clarification for release factors (water, air)

The estimated release factors for this Exposure Scenario are based on the Operational Conditions (OCs) and the Risk Management Measures (RMMs) as listed below.

Operational Conditions

Indoor use is described here. The process is optimized for highly efficient use of raw material which leads to a very minimal environmental release. The processes are performed without water contact. Wastewater emissions are only generated from equipment cleaning with water.

Risk Management Measures

On-site technology for air emission reduction takes place for indoor applications. Appropriate air removal techniques to achieve the required emission reduction are listed below.

- Wet scrubber (gas removal): typical efficiency of 70 %
- Thermal oxidation: typical efficiency of 98 %
- Vapour recovery (adsorption): typical efficiency of 80 %

Wastewater is treated by on-site and/or off-site STP which ensures a typical removal efficiency of at

least 87 % as predicted by the simple treat model (Technical Guidance Document on Risk Assessment, Part II, 2003) and by CHESAR (v2.2). The wastewater treatment techniques are based on separation techniques (sedimentation, oil-water separation) and biological treatment techniques (aerobic/anaerobic digestion processes, nitrification/denitrification).

Releases to waste

Release factor to waste from the process: 0 %

No initial release to waste is given.

9.7.1.3. Exposure and risks for the environment and man via the environment

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 208. Exposure concentrations and risks for the environment

Protection target	Exposure concentration	Risk characterisation
Freshwater	**Local PEC:** 1.394 mg/L	RCR = 0.046
Sediment (freshwater)	**Local PEC:** 5.352 mg/kg dw	RCR = 0.046
Marine water	**Local PEC:** 0.139 mg/L	RCR = 0.046
Sediment (marine water)	**Local PEC:** 0.535 mg/kg dw	RCR = 0.046
Sewage treatment plant	**Local PEC:** 13.89 mg/L	RCR = 0.113
Agricultural soil	**Local PEC:** 0.095 mg/kg dw	RCR < 0.01
Man via Environment - Inhalation	**Local PEC:** 0.821 mg/m³	RCR = 0.055
Man via Environment - Oral	**Exposure via food consumption:** 0.192 mg/kg bw/day	RCR = 0.479
Man via environment - combined routes		RCR = 0.534

Table 209. Contribution to oral intake for man via the environment from local contribution

Type of food	Estimated daily dose	Concentration in food
Drinking water	0.015 mg/kg bw/day	0.526 mg/L
Fish	7.592E-4 mg/kg bw/day	0.462 mg/kg ww
Leaf crops	0.173 mg/kg bw/day	10.1 mg/kg ww
Root crops	0.003 mg/kg bw/day	0.49 mg/kg ww
Meat	2.774E-6 mg/kg bw/day	6.45E-4 mg/kg ww
Milk	5.169E-5 mg/kg bw/day	0.006 mg/kg ww

Conclusion on risk characterisation

The results of the calculation with the given data show, that the industrial use of the substance with the corresponding SpERC can be considered to be of acceptable risk for the environment, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.7.2. Worker contributing scenario 1: Use in closed process, no likelihood of exposure (PROC 1)

9.7.2.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1.89E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed system (minimal contact during routine operations)	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374) [Effectiveness Dermal: 80 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 45 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.7.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 210. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, long-term	**0.03 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**0.122 mg/m³** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, long-term	**0.007 mg/kg bw/day** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.002 mg/cm²** (TRA Worker v3)	RCR < 0.01
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.011

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Combined routes, systemic, acute		RCR < 0.01 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.7.3. Worker contributing scenario 2: Use in closed, continuous process with occasional controlled exposure (PROC 2)

9.7.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1.89E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 15 minutes	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed continuous process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 45 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands face (480 cm^2)	TRA Worker v3

9.7.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 211. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.076 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, systemic, acute	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, long-term	**0.076 mg/m³** (TRA Worker v3)	RCR < 0.01
Inhalation, local, acute	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.102
Dermal, systemic, long-term	**0.007 mg/kg bw/day** (TRA Worker v3)	RCR < 0.01
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**9.99E-4 mg/cm²** (TRA Worker v3)	RCR < 0.01
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.014
Combined routes, systemic, acute		RCR = 0.102 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.7.4. Worker contributing scenario 3: Use in closed batch process (synthesis or formulation) (PROC 3)

9.7.4.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
• Vapour pressure at elevated temperature: < 1.89E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	

	Method
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 90 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 45 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.7.4.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 212. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.152 mg/m³** (TRA Worker v3)	RCR = 0.01
Inhalation, systemic, acute	**0.609 mg/m³** (TRA Worker v3)	RCR = 0.02
Inhalation, local, long-term	**0.152 mg/m³** (TRA Worker v3)	RCR = 0.01
Inhalation, local, acute	**0.609 mg/m³** (TRA Worker v3)	RCR = 0.02
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Worker v3)	RCR = 0.044
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.038
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.054
Combined routes, systemic, acute		RCR = 0.02 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management

Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.7.5. Worker contributing scenario 4: Industrial spraying (PROC 7)

9.7.5.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	TRA Worker v3
• Vapour pressure at elevated temperature: < 1E4 Pa *10001 Pa is a default value corresponding to the highest volatility band for a liquid substance in TRA. Thus a worst case exposure inhalation concentration is calculated if the user has no further information on the vapour pressure at elevated temperature. The extrapolation of the vapour pressure at elevated temperature according to equation (1) of the RIVM Report (No. 601900005/2004) results in a vapour pressure > 10000 Pa. Due to the fact that the modelling tool automatically applies the highest fugacity band for substances handled at elevated temperatures (see section above), the automatically provided vapour pressure of 10001 Pa does not need to be modified. An increased vapour pressure would have no influence on the exposure estimation. Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 95 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
• Automated process: Yes	Not applicable
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: No	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 250 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands and upper wrists (1500 cm^2)	TRA Worker v3

9.7.5.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 213. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	Not relevant	Qualitative (see below)
Inhalation, systemic, acute	Not relevant	Qualitative (see below)
Inhalation, local, long-term	Not relevant	Qualitative (see below)
Inhalation, local, acute	Not relevant	Qualitative (see below)
Dermal, systemic, long-term	Not relevant	Qualitative (see below)
Dermal, systemic, acute	Not relevant	Qualitative (see below)
Dermal, local, long-term	Not relevant	Qualitative (see below)
Dermal, local, acute	Not relevant	Qualitative (see below)
Eye, local	Not relevant	Qualitative (see below)
Combined routes, systemic, long-term	Not relevant	Qualitative (see below)
Combined routes, systemic, acute	Not relevant	Qualitative (see below)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

In this case, industrial spraying (PROC 7) is performed as automated process. The operators control room is enclosed and separated from this process. As a consequence, PROC 7 does not need to be assessed separately because any exposure referring to this spray application can be excluded. Other processes related to this automated spray application (i.e. cleaning and maintenance) are covered by PROC 1, PROC 2 and PROC 3 which has been assessed.

An exact process description is given as follows.
The piping system containing the mixture connects automatically with the on-line spraying system installed on top of the glass coating production line. The spraying machine is automatised and the solution is pulverised on line in a move from left to right of the float (speed of on-line spray: 5m/sec). It is controlled by distance by the operators that are located in an enclosed control room away from the DMF mixture exposure zone.
The temperature on-line during the spraying process varies between 200-250 °C. At this temperature, the DMF contained in the mixture vapourises, degrades and is taken away by the air flow spread on line at 5000 Nm^3/hr to the mouth of the thermal oxidation installation.
The industrial spraying is performed in an enclosed system which is depressurized. The mixture's vapours can therefore not escape the production process. At the mouth of the thermal oxidation installation, the atmosphere is aspired (20 000 Nm^3/hr - an air flow meter connected to the control room is installed at the level of the LEV) which immediately drives the DMF vapour in the air treatment system. Therefore, the final coated glass product does not contain DMF.

In conclusion, industrial spraying as automated process where any exposure to workers can be excluded is considered to be of acceptable risk for workers.

9.8. Exposure scenario 8: Use at industrial site - Industrial use for the manufacture of perfumes / fragrances

Sector of use:
SU 9, Manufacture of fine chemicals (SU 3: Industrial use)
SU 0, Other (SU 3: Industrial use)

Environment contributing scenario(s):	
Industrial use of substances in closed systems	ERC 7
Worker contributing scenario(s):	
Use in closed batch process (synthesis or formulation)	PROC 3
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities	PROC 8b

9.8.1. Environmental contributing scenario 1: Industrial use of substances in closed systems

9.8.1.1. Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily use at site: **Confidential information**
• Annual use at a site: **Confidential information**
• Percentage of tonnage used at regional scale: **Confidential information**
Conditions and measures related to sewage treatment plant
• Municipal STP: Yes [Effectiveness Water: 87.37 %]
• Discharge rate of STP: ≥ 2E3 m^3/d
• Application of the STP sludge on agricultural soil: No
Conditions and measures related to treatment of waste (including article waste)
• Particular considerations on the waste treatment operations: No (low risk) (ERC based assessment demonstrating control of risk with default conditions. Low risk assumed for waste life stage. Waste disposal according to national/local legislation is sufficient.)
Other conditions affecting environmental exposure
• Receiving surface water flow rate: ≥ 1.8E4 m^3/d

9.8.1.2. Releases

The local releases to the environment are reported in the following table.

Table 214. Local releases to the environment

Release	Release factor estimation method	Explanation / Justification
Water	ERC based	**Initial release factor:** 5 % **Final release factor:** 5 % **Local release rate:** **Confidential information**
Air	ERC based	**Initial release factor:** 5 % **Final release factor:** 5 % **Local release rate:** **Confidential information**

Release	Release factor estimation method	Explanation / Justification
Soil	ERC based	**Final release factor:** 5 %

Further clarification for release factors

As indicated by the applied ERC, the substance need to be handled in a closed system (indoor use). On-site technology for air emission reduction should take place in order to ensure the assumed release factor. Wastewater need to be treated by on-site and/or off-site STP which ensures a typical removal efficiency of at least 87 % as predicted by the simple treat model (Technical Guidance Document on Risk Assessment, Part II, 2003) and by CHESAR (v2.2).

Releases to waste

Release factor to waste from the process: 0 %

No initial release to waste is given.

9.8.1.3. Exposure and risks for the environment and man via the environment

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 215. Exposure concentrations and risks for the environment

Protection target	Exposure concentration	Risk characterisation
Freshwater	**Local PEC:** 3.478 mg/L	RCR = 0.116
Sediment (freshwater)	**Local PEC:** 13.35 mg/kg dw	RCR = 0.116
Marine water	**Local PEC:** 0.348 mg/L	RCR = 0.116
Sediment (marine water)	**Local PEC:** 1.335 mg/kg dw	RCR = 0.116
Sewage treatment plant	**Local PEC:** 34.73 mg/L	RCR = 0.282
Agricultural soil	**Local PEC:** 0.006 mg/kg dw	RCR < 0.01
Man via Environment - Inhalation	**Local PEC:** 0.038 mg/m³	RCR < 0.01
Man via Environment - Oral	**Exposure via food consumption:** 0.035 mg/kg bw/day	RCR = 0.087
Man via environment - combined routes		RCR = 0.089

Table 216. Contribution to oral intake for man via the environment from local contribution

Type of food	Estimated daily dose	Concentration in food
Drinking water	0.025 mg/kg bw/day	0.87 mg/L
Fish	0.002 mg/kg bw/day	1.043 mg/kg ww
Leaf crops	0.008 mg/kg bw/day	0.469 mg/kg ww
Root crops	1.699E-4 mg/kg bw/day	0.031 mg/kg ww
Meat	2.876E-7 mg/kg bw/day	6.687E-5 mg/kg ww
Milk	5.359E-6 mg/kg bw/day	6.687E-4 mg/kg ww

Conclusion on risk characterisation

The results of the calculation with the given data show, that the industrial use of the substance with the corresponding ERC can be considered to be of acceptable risk for the environment, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.8.2. Worker contributing scenario 1: Use in closed batch process (synthesis or formulation) (PROC 3)

9.8.2.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25 %	TRA Worker v3
• Vapour pressure at elevated temperature: < 2.532E3 Pa *The extrapolation of the vapour pressure at elevated temperature is based on equation (1) of the RIVM Report (No. 601900005/2004). Please refer to Appendix 1 of the respective CSR (submitted February 2014) for further information regarding vapour pressure extrapolation.*	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Closed batch process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 50 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.8.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 217. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.548 mg/m³** (TRA Worker v3)	RCR = 0.037
Inhalation, systemic, acute	**3.655 mg/m³** (TRA Worker v3)	RCR = 0.122
Inhalation, local, long-term	**0.548 mg/m³** (TRA Worker v3)	RCR = 0.037

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, local, acute	**3.655 mg/m³** (TRA Worker v3)	RCR = 0.122
Dermal, systemic, long-term	**0.012 mg/kg bw/day** (TRA Worker v3)	RCR = 0.016
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.004 mg/cm²** (TRA Worker v3)	RCR = 0.014
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.052
Combined routes, systemic, acute		RCR = 0.122 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.8.3. Worker contributing scenario 2: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b)

9.8.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95 %]	TRA Worker v3
• Respiratory Protection: Yes (Respirator with APF of 20) [Effectiveness Inhal: 95 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3

	Method
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.8.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 218. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.457 mg/m³** (TRA Worker v3)	RCR = 0.03
Inhalation, systemic, acute	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.102
Inhalation, local, long-term	**0.457 mg/m³** (TRA Worker v3)	RCR = 0.03
Inhalation, local, acute	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.102
Dermal, systemic, long-term	**0.686 mg/kg bw/day** (TRA Worker v3)	RCR = 0.868
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.05 mg/cm²** (TRA Worker v3)	RCR = 0.187
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.898
Combined routes, systemic, acute		RCR = 0.102 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the industrial use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.9. Exposure scenario 9: Use by professional worker - Professional use as laboratory agent

Sector of use:
SU 24, Scientific research and development (SU 22: Professional use)

Environment contributing scenario(s):	
Professional use as laboratory agent	ERC 8a
Worker contributing scenario(s):	
Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities	PROC 8a
Use as laboratory reagent	PROC 15

9.9.1. Environmental contributing scenario 1: Professional use as laboratory agent

9.9.1.1. Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily wide dispersive use: **Confidential information**
• Percentage of tonnage used at regional scale: = **Confidential information**
Conditions and measures related to sewage treatment plant
• Municipal STP: Yes [Effectiveness Water: 87.37 %]
• Discharge rate of STP: ≥ 2E3 m^3/d
• Application of the STP sludge on agricultural soil: Yes
Conditions and measures related to treatment of waste (including article waste)
• Particular considerations on the waste treatment operations: No (low risk) (ERC based assessment demonstrating control of risk with default conditions. Low risk assumed for waste life stage. Waste disposal according to national/local legislation is sufficient.)
Other conditions affecting environmental exposure
• Receiving surface water flow rate: ≥ 1.8E4 m^3/d

9.9.1.2. Releases

The local releases to the environment are reported in the following table.

Table 219. Local releases to the environment

Release	Release factor estimation method	Explanation / Justification
Water	ERC based	**Initial release factor:** 100 % **Final release factor:** 100 % **Local release rate:** **Confidential information**
Air	ERC based	**Initial release factor:** 100 % **Final release factor:** 100 %
Soil	ERC based	**Final release factor:** 0 %

Releases to waste

Release factor to waste from the process: 0 %

No initial release to waste is given.

9.9.1.3. Exposure and risks for the environment and man via the environment

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 220. Exposure concentrations and risks for the environment

Protection target	Exposure concentration	Risk characterisation
Freshwater	**Local PEC:** 0.008 mg/L	RCR < 0.01
Sediment (freshwater)	**Local PEC:** 0.031 mg/kg dw	RCR < 0.01
Marine water	**Local PEC:** 7.506E-4 mg/L	RCR < 0.01
Sediment (marine water)	**Local PEC:** 0.003 mg/kg dw	RCR < 0.01
Sewage treatment plant	**Local PEC:** 0.035 mg/L	RCR < 0.01
Agricultural soil	**Local PEC:** 0.002 mg/kg dw	RCR < 0.01
Man via Environment - Inhalation	**Local PEC:** 4.842E-5 mg/m³	RCR < 0.01
Man via Environment - Oral	**Exposure via food consumption:** 3.445E-4 mg/kg bw/day	RCR < 0.01
Man via environment - combined routes		RCR < 0.01

Table 221. Contribution to oral intake for man via the environment from local contribution

Type of food	Estimated daily dose	Concentration in food
Drinking water	2.7E-4 mg/kg bw/day	0.009 mg/L
Fish	1.57E-5 mg/kg bw/day	0.01 mg/kg ww
Leaf crops	1.042E-5 mg/kg bw/day	6.08E-4 mg/kg ww
Root crops	4.826E-5 mg/kg bw/day	0.009 mg/kg ww
Meat	1.938E-9 mg/kg bw/day	4.508E-7 mg/kg ww
Milk	3.613E-8 mg/kg bw/day	4.508E-6 mg/kg ww

Conclusion on risk characterisation

The results of the calculation with the given data show, that the professional use of the substance with the corresponding ERC can be considered to be of acceptable risk for the environment, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.9.2. Worker contributing scenario 1: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities (PROC 8a)

9.9.2.1. Conditions of use

	Method
Product (article) characteristics	

	Method
• Concentration of substance in mixture: 5-25%	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Good general ventilation (3-5 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 80 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Basic	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific employee training) [Effectiveness Dermal: 95 %]	Calculated manually
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Worker v3

9.9.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 222. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.384 mg/m³** (TRA Worker v3)	RCR = 0.026
Inhalation, systemic, acute	**2.558 mg/m³** (TRA Worker v3)	RCR = 0.085
Inhalation, local, long-term	**0.384 mg/m³** (TRA Worker v3)	RCR = 0.026
Inhalation, local, acute	**2.558 mg/m³** (TRA Worker v3)	RCR = 0.085
Dermal, systemic, long-term	**8.226 mg/kg bw/day** (TRA Worker v3) Manual modification: **8.226 mg/kg bw/day x 0.05 = 0.411 mg/kg bw/day**	RCR = 0.520
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.6 mg/cm²** (TRA Worker v3) Manual modification: **0.6 mg/cm² x 0.05 = 0.03 mg/cm²**	RCR = 0.112
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic,		RCR = 0.563

Route of exposure and type of effects	Exposure concentration	Risk characterisation
long-term		
Combined routes, systemic, acute		RCR = 0.085 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

Additional Risk Management Measures need to be considered for this process since laboratory staff is specifically educated for handling hazardous substances, so that a higher protection factor for dermal exposure is applied to account for specific activity training (APF20). This was calculated manually.

The results of the calculation with the given data show, that the professional use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9.9.3. Worker contributing scenario 2: Use as laboratory reagent (PROC 15)

9.9.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Worker v3
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	TRA Worker v3
• Containment: No	TRA Worker v3
• Local exhaust ventilation: yes [Effectiveness Inhal: 80 %]	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0 %]	TRA Worker v3
• Occupational Health and Safety Management System: Basic	TRA Worker v3
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with basic employee training) [Effectiveness Dermal: 90 %]	TRA Worker v3
• Respiratory Protection: No [Effectiveness Inhal: 0 %]	TRA Worker v3
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Worker v3
• Process temperature (for liquid): ≤ 40 °C	TRA Worker v3
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Worker v3

9.9.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 223. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, systemic, acute	**12.18 mg/m³** (TRA Worker v3)	RCR = 0.406
Inhalation, local, long-term	**3.046 mg/m³** (TRA Worker v3)	RCR = 0.203
Inhalation, local, acute	**12.18 mg/m³** (TRA Worker v3)	RCR = 0.406
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Worker v3)	RCR = 0.043
Dermal, systemic, acute		Qualitative (see below)
Dermal, local, long-term	**0.01 mg/cm²** (TRA Worker v3)	RCR = 0.037
Dermal, local, acute		Qualitative (see below)
Eye, local		Qualitative (see below)
Combined routes, systemic, long-term		RCR = 0.246
Combined routes, systemic, acute		RCR = 0.406 (only based on acute inhalation)

Conclusion on risk characterisation

The acute dermal exposure routes are sufficiently covered by the risk evaluation for long-term effects. Due to the fact that the substance is classified as Eye Irritant 2 (H 319), chemical goggles need to be worn to control exposure regarding local eye effects.

The results of the calculation with the given data show, that the professional use with the corresponding PROC can be considered to be of acceptable risk for workers, when the specified Risk Management Measures/Operational Conditions are implemented. Where other Risk Management Measures/Operational Conditions are adopted, then users should ensure that risks are managed to at least equivalent levels.

9a. TIER 2 EXPOSURE ASSESSMENT (and related risk characterisation)

9a.0. Introduction

Due to the fact that relevant measured data from several different industrial sites are available, a TIER 2 assessment was additionally elaborated.

Measured data by BASF were already submitted to ECHA via the document "BASF comments to the Draft background document for N,N-dimethylformamide (DMF), submitted by ECHA on 24 June 2013". In order to show that measured data are well below the Occupational Exposure Limits, the BASF workplace measurements are displayed below (see Table 286). Please refer to Appendix II of the respective CSR (submitted February 2014) for the full version of this document.

Table 224. BASF SE Worplace measurements (from "BASF comments to the Draft background document for N,N-dimethylformamide (DMF))

Manufacturing process step	Workplace concentration (e.g. mg/m3)	Basis for estimate (how measured or estimated)
Production - PROC 1, 2: Use in closed process, no likelihood of exposure	<0.09 – <0.12 mg/m³ Personnel shift mean value	Routine OEL Measurement of BASF (not detectable in 6 measurement between 2005 and 2010)
Production - PROC 1,2 : Use in closed process, no likelihood of exposure (Distillation)	<0.034 – <0.16 mg/m³ Personnel shift mean value	Routine OEL Measurement of BASF (not detectable in 12 measurement between 2005 and 2010)
Filling - PROC 8b: Transfer of substance or preparation (charging/ discharging) from/to vessels/large Containers at dedicated facilities	<0.28 – <0.64 mg/m³ Personnel shift mean value	Routine OEL Measurement of BASF (not detectable in 9 measurement between 2005 and 2010)
Filling - PROC 8b: Transfer of substance or preparation (charging/ discharging) from/to vessels/large	0,189 mg/m³ Shift mean value Personnel Peak value	Routine OEL Measurement of BASF. (1 single value with detectable DMF – usually DMF is not detectable)
Use as solvent in product synthesis at BASF. Includes PROC 1, 2, 3, 4, 8a, 8b	<0.034 - < 0.59 mg/m³ Personnel shift mean value	Routine OEL Measurement of BASF (not detectable in 10 measurement between 2005 and 2010)
Use for industrial cleaning (Ludwigshafen) Includes PROC 1, 2, 3, 4, 8a, 8b	< 0.11 - < 0.12 mg/m³	Routine OEL Measurement of BASF (not detectable in 3 measurement between 2005 and 2010)
Use for industrial cleaning (Ludwigshafen) Includes PROC 1, 2, 3, 4, 8a, 8b	4.2 -6.9 mg/m³ Personnel shift mean value	Routine OEL Measurement of BASF (detectable in 2 measurement between 2005 and 2010)
Use for industrial cleaning (Antwerp) Includes PROC 1, 2, 3, 4, 8a, 8b	2.7-3.0 mg/m³ Stationary	Routine OEL Measurement of BASF (detectable in 10 measurement between 1998 and 2001)
Use for industrial cleaning (Antwerp) Includes PROC 1, 2, 3, 4, 8a, 8b	< 0.2 mg/m³ Stationary	Routine OEL Measurement of BASF (not detectable in 3 measurement after introduction of new technical measurement in 2001-2011)
Use for industrial cleaning (Antwerp) Includes PROC 1, 2, 3, 4, 8a, 8b	<0.2 mg/m³ Personnel shift mean value	Routine OEL Measurement of BASF (not detectable in 19 measurement between 2001 and 2011)

Additional measured data by several industry sectors were gathered. These data are differentiated by the Identified Uses / Exposure Scenarios in which the information (measured workplace concentration) is correlated to specific processes (PROCs), Risk Management Measures (RMMs) and Operational Conditions (OCs). The Identified Uses are identical to the ones which are described in Chapter 9 of this document. An overview of all gathered (measured) data is provided in the table below.

Table 225. Overview of all measured data which has been provided by different Downstream Users (January 2014)

ES	Source of data	PROC	Concentration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	Remarks on measured data (as provided by data source)
1	A	8b	100	< 2 h	basic general ventilation	outdoor, ambient temperature	< 0.4 mg/m³	DMF concentration below analytical limit of quantification (< 0,4 mg/m³)
	A	8b	20 - 100	< 10 min	basic general ventilation	outdoor, ambient temperature	< 0.4 mg/m³	DMF concentration below analytical limit of quantification (< 0,4 mg/m³)
	A	15	20 - 100	< 8 h	enhanced general ventilation, LEV	indoor, ambient	< 0.4 mg/m³	DMF concentration below analytical limit of quantification (< 0,4 mg/m³)
2	B	3	20 - 80	< 1 h	basic general ventilation, LEV	indoor, < 50°C	< 0.5 mg/m³	no remarks provided
	B	4	20 - 80	< 4 h	basic general ventilation, LEV	indoor, < 40°C	< 0.5 mg/m³	no remarks provided
	B	5	20 - 80	< 2 h	basic general ventilation, LEV	indoor, < 50°C	< 0.5 mg/m³	no remarks provided
	B	9	100	< 1 h	basic general ventilation, LEV	indoor, ambient	< 0.5 mg/m³	no remarks provided
	B	15	100	< 4 h	LEV	indoor, 20 - 60°C	< 0.5 mg/m³	no remarks provided

Table 225. Overview of all measured data which has been provided by different Downstream Users (January 2014)

ES	Source of data	PROC	Concentration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	Remarks on measured data (as provided by data source)
3	C	15	> 25	< 8 h	enhanced general ventilation, LEV	indoor	≤ 3 mg/m³	no remarks provided
	C	3	100	< 8 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 0.4 ppm [1.2 mg/m³]	concentration below the analytical limit of quantification (0.4 ppm for VOC); PID detector has been used; continuous measurements for 1 hour (intervals of 30 seconds)
3	C	4	100	< 8 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 0.4 ppm [1.2 mg/m³]	concentration below the analytical limit of quantification (0.4 ppm for VOC); PID detector has been used; continuous measurements for 1 hour (intervals of 30 seconds)
	C	15	100	< 8 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 0.4 ppm [1.2 mg/m³]	concentration below the analytical limit of quantification (0.4 ppm for VOC); PID detector has been used; continuous measurements for 1 hour (intervals of 30 seconds)
	D	1	> 25	< 8 h	enhanced general ventilation, LEV	indoor, 50 - 140°C	0.002 - 1.8 mg/m³	Measurements were performed 2009, 2011 and 2013. The measurements were taken in the room ventilation system, where air is drawn out at the bottom of the building via big exhaust fans. The flow in the chimney is measured in order to ensure a laminar flow, before the TD-tube (Thermal Desorption) is inserted. The TD-tube is placed in the chimney and a pump is connected to active draw air into the tube. This is done for an hour and three consecutive measurements

Table 225. Overview of all measured data which has been provided by different Downstream Users (January 2014)

ES	Source of data	PROC	Concentration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	Remarks on measured data (as provided by data source)
								are taken. A GC-MS apparatus is used to determine the concentration of the substances in the air. Sampling is done according to DS/EN 13649 "Stationary Source Emissions – Determination of the mass concentration of individual gaseous compounds". [1. Udgave 2001-12-14, Dansk Standard] Analytical method used corresponds to EPA/625/R-96/010b - Compendium of Methods for the Determination of Toxic Organic Compounds in Ambient Air, Second Edition, Compendium Method TO-17, Determination of Volatile Organic Compounds in Ambient Air Using Active Sampling. Deviation from method: 3-bed sorbent tubes are used. Provided by Markes: Metal tube 5240 – Tenax TA/Carbopack X/UniCarb.
4	E	3	100	< 1 min	no RMMs provided	outdoor, ambient temperature	5 ppm [15 mg/m³]	peak exposure
	F	8b	100	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 0.1 mg/m³	based on limited number of samples

Table 225. Overview of all measured data which has been provided by different Downstream Users (January 2014)

ES	Source of data	PROC	Concentration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	Remarks on measured data (as provided by data source)
	G	3	100	< 8 h	basic general ventilation, LEV	indoor, ≤ 100 °C	< OEL	The available data are more than 10 years old.
	H	8b	100	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 0.79 ppm [2.37 mg/m³]	Personal monitoring in operator breathing zone using 3M - 3500 passive badge - Analysis by Gas Chromatography O8(U) UKAS Accredited
	H	8b	1 - 5	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	0.81 mg/m³	Personal monitoring in operator breathing zone using 3M - 3500 passive badge - Analysis by Gas Chromatography O8(U) UKAS Accredited (8h TWA)
	H	8b	< 1	< 15 min	enhanced general ventilation, LEV	indoor, ambient temperature	0.6 ppm [1.8 mg/m³]	Personal monitoring in operator breathing zone using 3M - 3500 passive badge - Analysis by Gas Chromatography O8(U) UKAS Accredited (8 h TWA)
	I	8b	100	< 1 h	basic general ventilation, LEV	indoor, ambient temperature	≤ 0.2 mg/m³	no remarks provided
	J	1	> 25	< 8 h	enhanced general ventilation	indoor, 20 - 100°C	< 0.01 mg/m³	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
	J	1	5 - 25	< 8 h	enhanced general ventilation	indoor, 20 - 100°C	< 0.01 mg/m³	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
4	J	1	1 - 5	< 8 h	enhanced general ventilation	indoor, 20 - 100°C	< 0.01 mg/m³	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)

Table 225. Overview of all measured data which has been provided by different Downstream Users (January 2014)

ES	Source of data	PROC	Concentration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	Remarks on measured data (as provided by data source)
	J	1	> 25	< 4 h	enhanced general ventilation	indoor, 100°C	< 15 mg/m³	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
	J	3	> 25	< 8 h	enhanced general ventilation	indoor, 20 - 100°C	< 0.01 mg/m³	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
	J	3	5 - 25	< 8 h	enhanced general ventilation	indoor, 20 - 100°C	< 0.01 mg/m³	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
	J	3	1 - 5	< 8 h	enhanced general ventilation	indoor, 20 - 100°C	< 0.01 mg/m³	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
	J	4	> 25	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 15 mg/m³	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
	J	4	5 - 25	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 15 mg/m³	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.

Table 225. Overview of all measured data which has been provided by different Downstream Users (January 2014)

ES	Source of data	PROC	Concentration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	Remarks on measured data (as provided by data source)
	J	4	1 - 5	< 1 h	enhanced general ventilation	indoor, ambient temperature	< 15 mg/m³	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
4	J	8a	> 25	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 15 mg/m³	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
	J	8a	5 - 25	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 15 mg/m³	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
	J	8a	1 - 5	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 15 mg/m³	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
	J	8b	100	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 15 mg/m³	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.

Table 225. Overview of all measured data which has been provided by different Downstream Users (January 2014)

ES	Source of data	PROC	Concentration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	Remarks on measured data (as provided by data source)
	J	9	100	< 1 h	enhanced general ventilation, LEV	indoor, ambient temperature	< 15 mg/m³	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
	J	15	100	< 8 h	good general ventilation, LEV	indoor, ambient temperature	< 0.01 mg/m³	DMF concentration below analytical limit of quantification (< 0.01 mg/m³);
4	K	2	80 - 100	< 1 h	fume hood, LEV	indoor, ambient temperature	< OEL	Occupational hygiene monitoring was performed by using Draeger DMF 183 (QC 30617 exp. 6.2016) tubes for the operations performed such as opening the DMF drum. EH 40 gives DMF 8 hr TWA = 5 ppm and STEL = 10 ppm. No colour change was observed during the monitoring.
5	B	3	20 - 80	< 2 h	basic general ventilation, LEV	indoor, 30 - 70°C	< 0.5 mg/m³	no remarks provided
	B	4	20 - 80	< 6 h	basic general ventilation, LEV	indoor, < 55°C	< 0.5 mg/m³	no remarks provided
	L	8b	100	< 1 h	basic general ventilation, LEV	indoor, ambient temperature	0.8 mg/m³	DE concentration
	L	1	> 25	< 8 h	basic general ventilation, LEV	indoor, 100°C	0.8 mg/m³	DE concentration

Table 225. Overview of all measured data which has been provided by different Downstream Users (January 2014)

ES	Source of data	PROC	Concentration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	Remarks on measured data (as provided by data source)
	M	9	> 25	< 4 h	good general ventilation, LEV	indoor, 30 - 60°C	0.2 - 0.5 mg/m³	Packaging. Last monitoring in 2011.
	N	3	> 25	< 8 h	enhanced general ventilation	indoor, 55°C	1.63 mg/m³	2013 Measure : full shift (8h) - sensor carried by the operator
	N	4	> 25	< 1 h	enhanced general ventilation, LEV	indoor, 30°C	9 mg/m³	2013 Measure : mean value of 15 min of operator's exposure - sensor carried by operator
	N	4	> 25	< 8 h	enhanced general ventilation, LEV	indoor, 130°C	9 mg/m³	Mean of 2011,2012 Measures : mean value of 8h operator exposure - sensor carried by operator
	N	2	1 - 5	< 8 h	enhanced general ventilation, LEV	indoor, 90°C	1.22 mg/m³	2013 Measure : full shift (8h) - sensor carried by the operator
	N	4	< 1	< 8 h	enhanced general ventilation, LEV	indoor, 50°C	7 mg/m³	2012 Measure : mean value for full shift (8h) exposure - sensor carried by the operator
5	N	3	> 25	< 15 min	basic general ventilation, LEV	indoor, 70°C	27 mg/m³	2013 Measure : mean value of 15 min of operator's exposure - sensor carried by operator
	N	4	5 - 25	< 15 min	enhanced general ventilation, LEV	indoor, ambient temperature	10.5 mg/m³	Mean of 2012 Measure : mean value of 15 min of operator's exposure - sensor carried by operator

Table 225. Overview of all measured data which has been provided by different Downstream Users (January 2014)

ES	Source of data	PROC	Concentration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	Remarks on measured data (as provided by data source)
	N	2	5 - 25	< 8 h	enhanced general ventilation, LEV	indoor, 90°C	7.5 mg/m³	Mean of 2012 Measure : mean value for full shift (8h) exposure - sensor carried by the operator
	N	4	1 - 5	< 1 h	LEV	indoor, ambient temperature	27 mg/m³	2012 Measure : mean value of 1 hour of operator's exposure - sensor carried by operator
	O	4	5 - 25	< 8 h	basic general ventilation, LEV	indoor, ambient temperature	< 0.01 mg/m³	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
	O	5	> 25	< 1 h	basic general ventilation, LEV	indoor, ambient temperature	≤ 7.1 ppm [21.3 mg/m³]	maximum concentration
	P	2	> 25	continuous	basic general ventilation, LEV	indoor, ambient temperature	0 - 2 ppm [0 – 6 mg/m³]	Concentration continuously monitored by fixed PID monitors. DMF detector tube readings are taken every shift.
6	L	8b	100	< 1 h	basic general ventilation, LEV	indoor, ambient temperature	0.8 mg/m³	DE concentration
	L	1	> 25	< 8 h	basic general ventilation, LEV	indoor, 100°C	0.8 mg/m³	DE concentration

Table 225. Overview of all measured data which has been provided by different Downstream Users (January 2014)

ES	Source of data	PROC	Concentration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	Remarks on measured data (as provided by data source)
7	Q	1	> 25	< 15 min	basic general ventilation	indoor, 45°C	< 0.3 mg/m³	The air concentration is reported as below the detection limit of the analytical method (< 0.3 mg/m³). The sampling was performed according to EN689 in active mode with a specific sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific absorbent for the sampling of the gaseous fraction. After the elution, the analysis was performed by GC-FID according to NF X 43-267 method. Number of measured data point: 3
7	Q	2	> 25	< 15 min	basic general ventilation	indoor, 45°C	0.36 mg/m³	The air concentration is reported as below the detection limit of the analytical method (< 0.3 mg/m³). The sampling was performed according to EN689 in active mode with a specific sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific absorbent for the sampling of the gaseous fraction. After elution, the analysis was performed by GC-FID according to NF X 43-267 method. Number of measured data point: 3

Table 225. Overview of all measured data which has been provided by different Downstream Users (January 2014)

ES	Source of data	PROC	Concentration of substance [%]	Duration of exposure	RMMs*	OCs	Measured workplace concentration	Remarks on measured data (as provided by data source)
	Q	3	> 25	< 15 min	basic general ventilation, LEV	indoor, 45°C	< 0.3 mg/m³	The air concentration is reported as below the detection limit of the analytical method (< 0.3 mg/m³). The sampling was performed according to EN689 in active mode with a specific sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific absorbent for the sampling of the gaseous fraction. After elution, the analysis was performed by GC-FID according to NF X 43-267 method. Number of measured data point: 3
	Q	7	> 25	< 4 h	basic general ventilation, LEV	indoor, 250°C	< 0.3 mg/m³	The air concentration is reported as below the detection limit of the analytical method (< 0.3 mg/m³). The sampling was performed according to EN689 in active mode with a specific sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific absorbent for the sampling of the gaseous fraction. After elution, the analysis was performed by GC-FID according to NF X 43-267 method. Number of measured data point: 3
8	No measured data available							
9	No measured data available							

* basic general ventilation refers to 1 - 3 air changes per hour
good general ventilation refers to 3 - 5 air changes per hour

enhanced general ventilation refers to 5 - 10 air changes per hour

9a.0.1. Workers

Scope and type of assessment

The scope of exposure assessment and type of risk characterisation required for workers are described in the following table. Based on the performed measurements, only inhalation exposure (systemic long-term and systemic acute) is evaluated here.

Table 226. Type of risk characterisation required for workers

Route	Type of effect	Type of risk characterisation	Hazard conclusion (see section 5.11)
Inhalation	Systemic Long Term	Quantitative	DNEL (Derived No Effect Level) = 15 mg/m³
	Systemic Acute	Quantitative	DNEL (Derived No Effect Level) = 30 mg/m³

9a.1. Exposure scenario 1: Manufacture - Manufacture of substance

9a.1.1. Worker contributing scenario 1: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b)

9a.1.1.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH (Human Health)
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	Measured HH
Other conditions affecting workers exposure	
• Place of use: Outdoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.1.1.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 227. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.4 mg/m³** (Measured HH)	RCR = 0.027

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as below the analytical limit of quantification (< 0.4 mg/m³).

9a.1.2. Worker contributing scenario 2: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b)

9a.1.2.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 15 minutes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Outdoor	Measured HH

	Method
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.1.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 228. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.4 mg/m³** (Measured HH)	RCR = 0.027

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as below the analytical limit of quantification (< 0.4 mg/m³).

9a.1.3. Worker contributing scenario 3: Use as laboratory reagent (PROC 15)

9a.1.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• Local exhaust ventilation: yes	Measured HH
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.1.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 229. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.4 mg/m³** (Measured HH)	RCR = 0.027

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as below the analytical limit of quantification (< 0.4 mg/m³).

9a.2. Exposure scenario 2: Formulation - Formulation of substance

9a.2.1. Worker contributing scenario 1: Use in closed batch process (synthesis or formulation) (PROC 3)

9a.2.1.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 50 °C	Measured HH

9a.2.1.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 230. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.5 mg/m³** (Measured HH)	RCR = 0.033

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as < 0.5 mg/m³.

9a.2.2. Worker contributing scenario 2: Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4)

9a.2.2.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	Measured HH
Technical and organisational conditions and measures	

	Method
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.2.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 231. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.5 mg/m³** (Measured HH)	RCR = 0.033

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as < 0.5 mg/m³.

9a.2.3. Worker contributing scenario 3: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) (PROC 5)

9a.2.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 50 °C	Measured HH

9a.2.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 232. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.5 mg/m³** (Measured HH)	RCR = 0.033

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as < 0.5 mg/m³.

9a.2.4. Worker contributing scenario 4: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) (PROC 9)

9a.2.4.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.2.4.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 233. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.5 mg/m³** (Measured HH)	RCR = 0.033

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as < 0.5 mg/m³.

9a.2.5. Worker contributing scenario 5: Use as laboratory reagent (PROC 15)

9a.2.5.1. Conditions of use

	Method

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	Measured HH
Technical and organisational conditions and measures	
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 60 °C	Measured HH

9a.2.5.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 234. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.5 mg/m³** (Measured HH)	RCR = 0.033

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as < 0.5 mg/m³.

9a.3. Exposure scenario 3: Use at industrial site - Industrial use for the production of fine chemicals

9a.3.1. Worker contributing scenario 1: Use in closed process, no likelihood of exposure (PROC 1)

9a.3.1.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 140 °C	Measured HH

9a.3.1.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 235. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.8 mg/m³** (Measured HH)	RCR = 0.12

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as 0.002 - 1.8 mg/m³. The highest air concentration was used to calculate the Risk Characterisation Ratio. Measurements were performed 2009, 2011 and 2013. The measurements were taken in the room ventilation system, where air is drawn out at the bottom of the building via big exhaust fans. The flow in the chimney is measured in order to ensure a laminar flow, before the TD-tube (Thermal Desorption) is inserted. The TD-tube is placed in the chimney and a pump is connected to active draw air into the tube. This is done for an hour and three consecutive measurements are taken. A GC-MS apparatus is used to determine the concentration of the substances in the air.

  Sampling is done according to DS/EN 13649 “Stationary Source Emissions – Determination of the mass concentration of individual gaseous compounds”. [1. Udgave 2001-12-14, Dansk Standard]

Analytical method used corresponds to EPA/625/R-96/010b - Compendium of Methods for the Determination of Toxic Organic Compounds in Ambient Air, Second Editon, Compendium Method TO-17, Determination of Volatile Organic Compounds in Ambient Air Using Active Sampling.

Deviation from method: 3-bed sorbent tubes are used. Provided by Markes: Metal tube 5240 – Tenax TA/Carbopack X/UniCarb.

Note: The building in which the production equipment is placed is not where the workers usually stay. They are only out there on inspections rounds and occasionally to maintain equipment. The rest of the time they will be in the control room. Workers will maximally be in the production building 25-50% of the time (more likely 25%).

9a.3.2. Worker contributing scenario 2: Use in closed batch process (synthesis or formulation) (PROC 3)

9a.3.2.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.3.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 236. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.2 mg/m³** (Measured HH)	RCR = 0.08

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as below the analytical limit of quantification (0.4 ppm for VOC) which refers to 1.2 mg/m³. The analytical determination was performed by using a PID detector (continuous measurements for 1 hour, intervals of 30 seconds).

9a.3.3. Worker contributing scenario 3: Use in batch and other process (synthesis)

where opportunity for exposure arises (PROC 4)

9a.3.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.3.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 237. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.2 mg/m³** (Measured HH)	RCR = 0.08

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as below the analytical limit of quantification (0.4 ppm for VOC) which refers to 1.2 mg/m³. The analytical determination was performed by using a PID detector (continuous measurements for 1 hour, intervals of 30 seconds).

9a.3.4. Worker contributing scenario 4: Use as laboratory reagent (PROC 15)

9a.3.4.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH

	Method
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.3.4.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 238. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**3 mg/m³** (Measured HH)	RCR = 0.2

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The measured air concentration was reported as ≤ 3 mg/m³.

9a.3.5. Worker contributing scenario 5: Use as laboratory reagent (PROC 15)

9a.3.5.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.3.5.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 239. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.2 mg/m³** (Measured HH)	RCR = 0.08

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as below the analytical limit of quantification (0.4 ppm for VOC) which refers to 1.2 mg/m³. The analytical determination was performed by using a PID detector (continuous measurements for 1 hour, intervals of 30 seconds).

9a.4. Exposure scenario 4: Use at industrial site - Industrial use for the production of pharmaceuticals

9a.4.1. Worker contributing scenario 1: Use in closed process, no likelihood of exposure (PROC 1)

9a.4.1.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 100 °C	Measured HH

9a.4.1.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 240. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.01 mg/m³** (Measured HH)	RCR < 0.01

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as below the analytical limit of quantification (< 0.01 mg/m³).

9a.4.2. Worker contributing scenario 2: Use in closed process, no likelihood of exposure (PROC 1)

9a.4.2.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH

	Method
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 100 °C	Measured HH

9a.4.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 241. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.01 mg/m³** (Measured HH)	RCR < 0.01

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as below the analytical limit of quantification (< 0.01 mg/m³).

9a.4.3. Worker contributing scenario 3: Use in closed process, no likelihood of exposure (PROC 1)

9a.4.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 1-5 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 100 °C	Measured HH

9a.4.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 242. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.01 mg/m³** (Measured HH)	RCR < 0.01

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as below the analytical limit of quantification (< 0.01 mg/m³).

9a.4.4. Worker contributing scenario 4: Use in closed process, no likelihood of exposure (PROC 1)

9a.4.4.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 100 °C	Measured HH

9a.4.4.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 243. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term		Qualitative (see below)

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as below the OEL of 15 mg/m³. Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.

Conclusion on risk characterisation

Since it is reported that the air concentration is below the OEL of 15 mg/m³, this process is considered as safe.

9a.4.5. Worker contributing scenario 5: Use in closed, continuous process with occasional controlled exposure (PROC 2)

9a.4.5.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.5.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 244. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term		Qualitative (see below)

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  Occupational hygiene monitoring was performed by using Draeger DMF 183 (QC 30617 exp. 6.2016) tubes for the operations performed such as opening the DMF drum. EH 40 gives DMF 8 hr TWA = 5 ppm and STEL = 10 ppm. No colour change was observed during the monitoring.

Conclusion on risk characterisation

Since it is reported that the air concentration is below the OEL of 15 mg/m³, this process is considered as safe.

9a.4.6. Worker contributing scenario 6: Use in closed batch process (synthesis or formulation) (PROC 3)

9a.4.6.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 100 °C	Measured HH

9a.4.6.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 245. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term		Qualitative (see below)

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The available data show no exposure above the OEL (< 15 mg/m³). The available data is more than 10 years old.

Conclusion on risk characterisation

Since it is reported that the air concentration is below the OEL of 15 mg/m³, this process is considered as safe.

9a.4.7. Worker contributing scenario 7: Use in closed batch process (synthesis or formulation) (PROC 3)

9a.4.7.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	Measured HH

	Method
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 100 °C	Measured HH

9a.4.7.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 246. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.01 mg/m³** (Measured HH)	RCR < 0.01

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as below the analytical limit of quantification (< 0.01 mg/m³).

9a.4.8. Worker contributing scenario 8: Use in closed batch process (synthesis or formulation) (PROC 3)

9a.4.8.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 100 °C	Measured HH

9a.4.8.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 247. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic,	**0.01 mg/m³** (Measured HH)	RCR < 0.01

Route of exposure and type of effects	Exposure concentration	Risk characterisation
long-term		

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as below the analytical limit of quantification (< 0.01 mg/m³).

9a.4.9. Worker contributing scenario 9: Use in closed batch process (synthesis or formulation) (PROC 3)

9a.4.9.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 1-5 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 100 °C	Measured HH

9a.4.9.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 248. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.01 mg/m³** (Measured HH)	RCR < 0.01

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as below the analytical limit of quantification (< 0.01 mg/m³).

9a.4.10. Worker contributing scenario 10: Use in closed batch process (synthesis or formulation) (PROC 3)

9a.4.10.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 15 min	Measured HH
Other conditions affecting workers exposure	
• Place of use: Outdoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.10.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 249. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, acute	**15 mg/m³** (Measured HH)	RCR = 0.5

Remarks on exposure data

Measured HH

- Inhalation, systemic, acute:
  The workplace concentration was reported as 5 ppm which refers to 15 mg/m³. The concentration is considered as peak exposure.

9a.4.11. Worker contributing scenario 11: Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4)

9a.4.11.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.11.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 250. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term		Qualitative (see below)

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as below the OEL of 15 mg/m³. Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.

Conclusion on risk characterisation

Since it is reported that the air concentration is below the OEL of 15 mg/m³, this process is considered as safe.

9a.4.12. Worker contributing scenario 12: Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4)

9a.4.12.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.12.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 251. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term		Qualitative (see below)

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as below the OEL of 15 mg/m³. Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.

Conclusion on risk characterisation

Since it is reported that the air concentration is below the OEL of 15 mg/m³, this process is considered as safe.

9a.4.13. Worker contributing scenario 13: Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4)

9a.4.13.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 1-5 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.13.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 252. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term		Qualitative (see below)

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as below the OEL of 15 mg/m³. Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.

Conclusion on risk characterisation

Since it is reported that the air concentration is below the OEL of 15 mg/m³, this process is considered as safe.

9a.4.14. Worker contributing scenario 14: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities (PROC 8a)

9a.4.14.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.14.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 253. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term		Qualitative (see below)

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as below the OEL of 15 mg/m³. Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.

Conclusion on risk characterisation

Since it is reported that the air concentration is below the OEL of 15 mg/m³, this process is considered as safe.

9a.4.15. Worker contributing scenario 15: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities

(PROC 8a)

9a.4.15.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.15.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 254. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term		Qualitative (see below)

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as below the OEL of 15 mg/m³. Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.

Conclusion on risk characterisation

Since it is reported that the air concentration is below the OEL of 15 mg/m³, this process is considered as safe.

9a.4.16. Worker contributing scenario 16: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities (PROC 8a)

9a.4.16.1. Conditions of use

	Method
Product (article) characteristics	

	Method
• Concentration of substance in mixture: 1-5 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.16.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 255. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term		Qualitative (see below)

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as below the OEL of 15 mg/m³. Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.

Conclusion on risk characterisation

Since it is reported that the air concentration is below the OEL of 15 mg/m³, this process is considered as safe.

9a.4.17. Worker contributing scenario 17: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b)

9a.4.17.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	

	Method
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.17.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 256. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**2.37 mg/m³** (Measured HH)	RCR = 0.158

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as < 0.79 ppm which refers to 2.37 mg/m³ (Personal monitoring in operator breathing zone using 3M - 3500 passive badge - Analysis by Gas Chromatography O8(U) UKAS Accredited).

9a.4.18. Worker contributing scenario 18: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b)

9a.4.18.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.18.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 257. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.1 mg/m³** (Measured HH)	RCR < 0.01

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration was reported as < 0.1 mg/m³ which is based on a limited number of samples taken.

9a.4.19. Worker contributing scenario 19: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b)

9a.4.19.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.19.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 258. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, acute	**0.2 mg/m³** (Measured HH)	RCR < 0.01

Remarks on exposure data

Measured HH

- Inhalation, systemic, acute:
  The maximum air concentration was reported as < 0.2 mg/m³.

9a.4.20. Worker contributing scenario 20: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities

(PROC 8b)

9a.4.20.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.20.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 259. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term		Qualitative (see below)

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as below the OEL of 15 mg/m³. Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.

Conclusion on risk characterisation

Since it is reported that the air concentration is below the OEL of 15 mg/m³, this process is considered as safe.

9a.4.21. Worker contributing scenario 21: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b)

9a.4.21.1. Conditions of use

	Method
Product (article) characteristics	

	Method
• Concentration of substance in mixture: 1-5 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.21.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 260. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.81 mg/m³** (Measured HH)	RCR = 0.054

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration (8h TWA) was reported as < 0.81 mg/m³. (Personal monitoring in operator breathing zone using 3M - 3500 passive badge - Analysis by Gas Chromatography O8(U) UKAS Accredited).

9a.4.22. Worker contributing scenario 22: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b)

9a.4.22.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: < 1 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 15 minutes	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH

	Method
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.22.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 261. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.8 mg/m³** (Measured HH)	RCR = 0.12

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration (8h TWA) was reported as 0.6 ppm which refers to 1.8 mg/m³. (Personal monitoring in operator breathing zone using 3M - 3500 passive badge - Analysis by Gas Chromatography O8(U) UKAS Accredited).

9a.4.23. Worker contributing scenario 23: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) (PROC 9)

9a.4.23.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.23.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 262. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term		Qualitative (see below)

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as below the OEL of 15 mg/m³. Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.

Conclusion on risk characterisation

Since it is reported that the air concentration is below the OEL of 15 mg/m³, this process is considered as safe.

9a.4.24. Worker contributing scenario 24: Use as laboratory reagent (PROC 15)

9a.4.24.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Good general ventilation (3-5 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.4.24.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 263. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.1 mg/m³** (Measured HH)	RCR < 0.01

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as below the analytical limit of quantification (< 0.01 mg/m³).

9a.5. Exposure scenario 5: Use at industrial site - Industrial use for the production of polymers

9a.5.1. Worker contributing scenario 1: Use in closed process, no likelihood of exposure (PROC 1)

9a.5.1.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 100 °C	Measured HH

9a.5.1.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 264. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.8 mg/m³** (Measured HH)	RCR = 0.053

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as 0.8 mg/m³.

9a.5.2. Worker contributing scenario 2: Use in closed, continuous process with occasional controlled exposure (PROC 2)

9a.5.2.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 1-5 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	

	Method
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 90 °C	Measured HH

9a.5.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 265. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.22 mg/m³** (Measured HH)	RCR = 0.081

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as 1.22 mg/m³. The measurements were performed in 2013 with a sensor carried by the operator (8h shift).

9a.5.3. Worker contributing scenario 3: Use in closed, continuous process with occasional controlled exposure (PROC 2)

9a.5.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 90 °C	Measured HH

9a.5.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 266. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**7.5 mg/m³** (Measured HH)	RCR = 0.5

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as 7.5 mg/m³. The measurements were performed in 2012 with a sensor carried by the operator (mean value for 8h shift).

9a.5.4. Worker contributing scenario 4: Use in closed, continuous process with occasional controlled exposure (PROC 2)

9a.5.4.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: continuous process	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.5.4.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 267. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**6 mg/m³** (Measured HH)	RCR = 0.4

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as 0 - 2 ppm which refers to 0 - 6 mg/m³. The air concentration is continuously monitored by fixed PID. Detector tube readings are taken every shift.

9a.5.5. Worker contributing scenario 5: Use in closed batch process (synthesis or formulation) (PROC 3)

9a.5.5.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 70 °C	Measured HH

9a.5.5.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 268. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.5 mg/m³** (Measured HH)	RCR = 0.033

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as < 0.5 mg/m³.

9a.5.6. Worker contributing scenario 6: Use in closed batch process (synthesis or formulation) (PROC 3)

9a.5.6.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH

	Method
• Process temperature (for liquid): ≤ 55 °C	Measured HH

9a.5.6.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 269. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.63 mg/m³** (Measured HH)	RCR = 0.109

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as 1.63 mg/m³. The measurements were performed in 2013 with a sensor carried by the operator (8h shift).

9a.5.7. Worker contributing scenario 7: Use in closed batch process (synthesis or formulation) (PROC 3)

9a.5.7.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 15 minutes	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 70 °C	Measured HH

9a.5.7.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 270. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, acute	**27 mg/m³** (Measured HH)	RCR = 0.9

Remarks on exposure data

Measured HH

- Inhalation, systemic, acute:
  The air concentration is reported as 27 mg/m³. The measurements were performed in 2013 with a sensor carried by the operator (mean value for short-term exposure of 15 minutes).

9a.5.8. Worker contributing scenario 8: Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4)

9a.5.8.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 55 °C	Measured HH

9a.5.8.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 271. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.5 mg/m³** (Measured HH)	RCR = 0.033

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as < 0.5 mg/m³.

9a.5.9. Worker contributing scenario 9: Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4)

9a.5.9.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	

	Method
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.5.9.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 272. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, acute	**9 mg/m³** (Measured HH)	RCR = 0.3

Remarks on exposure data

Measured HH

- Inhalation, systemic, acute:
  The air concentration is reported as 9 mg/m³. The measurements were performed in 2013 with a sensor carried by the operator (mean value for short-term exposure of 15 minutes).

9a.5.10. Worker contributing scenario 10: Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4)

9a.5.10.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 130 °C	Measured HH

9a.5.10.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 273. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**9 mg/m³** (Measured HH)	RCR = 0.6

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as 9 mg/m³. The measurements were performed in 2011 and 2012 with a sensor carried by the operator (mean value for 8h shift).

9a.5.11. Worker contributing scenario 11: Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4)

9a.5.11.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: <1 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 50 °C	Measured HH

9a.5.11.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 274. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**7 mg/m³** (Measured HH)	RCR = 0.467

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as 7 mg/m³. The measurements were performed in 2012 with a sensor carried by the operator (mean value for 8h shift).

9a.5.12. Worker contributing scenario 12: Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4)

9a.5.12.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 15 minutes	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.5.12.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 275. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, acute	**10.5 mg/m³** (Measured HH)	RCR = 0.35

Remarks on exposure data

Measured HH

- Inhalation, systemic, acute:
  The air concentration is reported as 10.5 mg/m³. The measurements were performed in 2012 with a sensor carried by the operator (mean value for short-term exposure of 15 minutes).

9a.5.13. Worker contributing scenario 13: Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4)

9a.5.13.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 5-25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH

	Method
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.5.13.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 276. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.01 mg/m³** (Measured HH)	RCR < 0.01

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as below the analytical limit of quantification (< 0.01 mg/m³).

9a.5.14. Worker contributing scenario 14: Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4)

9a.5.14.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: 1-5 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes [Effectiveness Inhal: 0 %]	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.5.14.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 277. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, acute	**27 mg/m³** (Measured HH)	RCR = 0.9

Remarks on exposure data

Measured HH

- Inhalation, systemic, acute:
  The air concentration was reported as 27 mg/m³ (mean value of 1 hour). The measurements were performed in 2012 with a sensor carried by the operator.

9a.5.15. Worker contributing scenario 15: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) (PROC 5)

9a.5.15.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.5.15.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 278. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, acute	**21.3 mg/m³** (Measured HH)	RCR = 0.71

Remarks on exposure data

Measured HH

- Inhalation, systemic, acute:
  The maximum air concentration is reported as 7.1 ppm which refers to 21.3 mg/m³. Since the maximum concentration was provided, this values is compared to the DNEL for inhalation, systemic, acute.

9a.5.16. Worker contributing scenario 16: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b)

9a.5.16.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	

	Method
• Duration of activity: < 1 hour	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.5.16.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 279. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.8 mg/m³** (Measured HH)	RCR = 0.053

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as 0.8 mg/m³.

9a.5.17. Worker contributing scenario 17: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) (PROC 9)

9a.5.17.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Good general ventilation (3-5 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 60 °C	Measured HH

9a.5.17.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 280. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.5 mg/m³** (Measured HH)	RCR = 0.033

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as 0.2 - 0.5 mg/m³. The measurements were performed in 2011.

9a.6. Exposure scenario 6: Use at industrial site - Industrial use for the production of textiles, leather and fur

9a.6.1. Worker contributing scenario 1: Use in closed process, no likelihood of exposure (PROC 1)

9a.6.1.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 100 °C	Measured HH

9a.6.1.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 281. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.8 mg/m³** (Measured HH)	RCR = 0.053

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as 0.8 mg/m³.

9a.6.2. Worker contributing scenario 2: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities (PROC 8b)

9a.6.2.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	Measured HH

	Method
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 40 °C	Measured HH

9a.6.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 282. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.8 mg/m³** (Measured HH)	RCR = 0.053

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  The air concentration is reported as 0.8 mg/m³.

9a.7. Exposure scenario 7: Use at industrial site - Industrial use for the manufacture of non-metallic mineral products

9a.7.1. Worker contributing scenario 1: Use in closed process, no likelihood of exposure (PROC 1)

9a.7.1.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 15 minutes	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 45 °C	Measured HH

9a.7.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 283. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.3 mg/m³** (Measured HH)	RCR = 0.02

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  Number of measured data point: 3
  The air concentration is reported as below the detection limit of the analytical method (< 0.3 mg/m³). The sampling was performed according to EN689 in active mode with a specific sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific absorbent for the sampling of the gaseous fraction. After elution, the analysis was performed by GC-FID according to NF X 43-267 method.

9a.7.2. Worker contributing scenario 2: Use in closed, continuous process with occasional controlled exposure (PROC 2)

9a.7.2.1. Conditions of use

	Method
Product (article) characteristics	

	Method
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 15 minutes	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: no [Effectiveness Inhal: 0 %]	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH
• Process temperature (for liquid): ≤ 45 °C	Measured HH

9a.7.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 284. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.4 mg/m³** (Measured HH)	RCR = 0.027

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  Number of measured data point: 3
  The air concentration is reported as 0.36 mg/m³). The sampling was performed according to EN689 in active mode with a specific sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific absorbent for the sampling of the gaseous fraction. After the elution, the analysis was performed by GC-FID according to NF X 43-267 method.

9a.7.3. Worker contributing scenario 3: Use in closed batch process (synthesis or formulation) (PROC 3)

9a.7.3.1. Conditions of use

	Method
Product (article) characteristics	
• Concentration of substance in mixture: >25 %	Measured HH
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 15 minutes	Measured HH
Technical and organisational conditions and measures	
• General ventilation: Basic general ventilation (1-3 air changes per hour)	Measured HH
• Local exhaust ventilation: yes	Measured HH
Other conditions affecting workers exposure	
• Place of use: Indoor	Measured HH

	Method
• Process temperature (for liquid): ≤ 45 °C	Measured HH

9a.7.4.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 285. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.3 mg/m³** (Measured HH)	RCR = 0.02

Remarks on exposure data

Measured HH

- Inhalation, systemic, long-term:
  Number of measured data point: 3
  The air concentration is reported as below the detection limit of the analytical method (< 0.3 mg/m³). The sampling was performed according to EN689 in active mode with a specific sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific absorbent for the sampling of the gaseous fraction. After the elution, the analysis was performed by GC-FID according to NF X 43-267 method.

9a.8. Exposure scenario 8: Use at industrial site - Industrial use for the manufacture of perfumes / fragrances

Measured data are not available for this Exposure Scenario.

9a.9. Exposure scenario 9: Use by professional worker - Professional use as laboratory agent

Measured data are not available for this Exposure Scenario.

10. RISK CHARACTERISATION RELATED TO COMBINED EXPOSURE

10.1. Human health

The combinations of exposure scenarios which could result in simultaneous exposure of humans can be excluded.

10.2. Environment (combined for all emission sources)

10.2.1. All uses (regional scale)

10.2.1.1. Total releases

The total releases to the environment from all the exposure scenarios covered are presented in the table below. This is the sum of the releases to the environments from all exposure scenarios addressed.

Table 286. Total releases to the environment per year from all life cycle stages:

Release route	Total releases per year
Water	**Confidential information**
Air	**Confidential information**
Soil	**Confidential information**

10.2.1.2. Regional exposure

Environment

The regional predicted environmental concentration (PEC regional) and the related risk characterisation ratios when a PNEC is available are presented in the table below.

The PEC regional have been estimated with EUSES.

Table 287. Predicted regional exposure concentrations (Regional PEC)

Protection target	Regional PEC	RCR
Freshwater	0.004 mg/L	< 0.01
Sediment (freshwater)	0.015 mg/kg dw	< 0.01
Marine water	4.033E-4 mg/L	< 0.01
Sediment (marine water)	0.001 mg/kg dw	< 0.01
Air	4.83E-5 mg/m³	Not applicable
Agricultural soil	0.002 mg/kg dw	< 0.01

Man via environment

The exposure to man via the environment from regional exposure and the related risk characterisation ratios are presented in the table below. The exposure concentration via inhalation is equal to the PEC air.

Table 288. Regional exposure to man via the environment

Route	Regional exposure	RCR
Inhalation	4.83E-5 mg/m³	< 0.01
Oral	2.151E-4 mg/kg bw/day	< 0.01
Combined routes		< 0.01

10.2.2. Local exposure due to all wide dispersive uses

Not relevant as there are not several wide dispersive uses covered in this CSR.

10.2.3. Local exposure due to combined uses at a site

The combinations of exposure scenarios which could result in simultaneous exposure of the environment can be excluded.

Annex B2: IFA (2012) MEGA-Auswertung zur Erstellung von REACH-Expositionsszenarien für N,N-Dimethylformamid

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MEGA-Auswertungen zur Erstellung von REACH- Expositionsszenarien für N,N-Dimethylformamid

1 Einleitung

Die Ermittlung und Dokumentation der im Folgenden ausgewerteten Messdaten von Expositionen am Arbeitsplatz erfolgte nach den Kriterien des Messsystems Gefährdungsermittlung der Unfallversicherungsträger – MGU[1] (ehemals BGMG). Ein Qualitätsmanagementsystem, das im Wesentlichen die Anforderungen der DIN EN ISO 9001 umsetzt, stellt den Standard des MGU sicher. Die Prüflaboratorien werden gemäß DIN EN ISO 17025 „Allgemeine Anforderungen an die Kompetenz von Prüf- und Kalibrierlaboratorien" betrieben.

Zur Bestimmung von in der Luft am Arbeitsplatz enthaltenem N,N-Dimethylformamid (CAS-Nummer: 68-12-2) wurden im Datenzeitraum von 2000 bis 2011 zwei validierte Verfahren eingesetzt:

- Analysenverfahren von 2000 bis 2007:
  Mittels einer Probenahmepumpe mit Röhrchenhalter wird ein definiertes Luftvolumen durch ein Silicagel-Röhrchen Typ ADS gesaugt. Nach der Extraktion mit alkalischem Methanol (Methanol mit 2 % KOH) erfolgt die qualitative und quantitative Bestimmung gaschromatographisch mit einem stickstoffselektiven Detektor (NSD). Die quantitative Bestimmung wird nach der Methode des internen Standards durchgeführt. Die Bestimmungsgrenze für das Standardverfahren im MGU betrug zu diesem Zeitpunkt 0,3 mg/m³ bei 40 l Probeluftvolumen.

- Analysenverfahren von 2007 bis 2011:
  Mittels einer Probenahmepumpe mit Röhrchenhalter wird ein definiertes Luftvolumen durch ein Aktivkohle-Röhrchen Typ B gesaugt. Nach der Extraktion mit Aceton/Wasser im Verhältnis von 98:2 erfolgt die qualitative und quantitative Bestimmung gaschromatographisch mit einem stickstoffselektiven Detektor (NSD). Die quantitative Bestimmung wird nach der Methode des internen Standards durchgeführt. Die Bestimmungsgrenze für das Standardverfahren im MGU beträgt 0,2 mg/m³ bei 40 l Probeluftvolumen. Quelle: MGU-Standardverfahren mit Stand 2012

Alle im MGU erhobenen Daten werden in der Expositionsdatenbank MEGA (Messdaten zur Exposition gegenüber Gefahrstoffen am Arbeitsplatz) zusammengeführt. Die vom IFA entwickelte MEGA^{Pro}-Software erlaubt die statistische Auswertung des Datenbestandes der Expositionsdatenbank MEGA nach unterschiedlichen Selektionskriterien und Auswertestrategien.

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[1] Gabriel, S.; Koppisch, D.; Range, D.: The MGU – a monitoring system for the collection and documentation of valid workplace exposure data. Gefahrstoffe – Reinhalt. Luft 70 (2010) Nr. 1/2, S. 43-49 http://www.dguv.de/ifa, Webcode d101507

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2 Datenlage und Auswertestrategie

2.1 Übersicht der im MGU ermittelten Messwerte, Datenzeitraum 2000 bis 2011

N,N-Dimethylformamid (CAS-Nummer: 68-12-2)
Standardverfahren im MGU
Luftproben mit Expositionsbezug

Für N,N-Dimethylformamid liegt in Deutschland ein Arbeitsplatzgrenzwert (AGW) von 15 mg/m³ vor.

Allgemeine Beschreibung	Anzahl Messwerte (%)
Insgesamt	223
Probenahmeart:	
stationär	125 (56 %)
an der Person	98 (44 %)
Anzahl Daten < Bestimmungsgrenze	92 (41 %)
Anzahl Daten > Grenzwert	28 (13 %)
Probenahme repräsentativ für:	
Expositionsdauer ≥ 6 h	164 (74 %)
Expositionsdauer < 6 h	47 (21 %)
Beispiele Expositionsbedingungen:	
Messplan:	
Arbeitsplatzmessungen	222 (99,6 %)
Innenraummessungen	1 (0,4 %)
Betriebliche Situation: ungünstig	17 (8 %)
Anlass der Messung: BK-Recherche	37 (17 %)
ohne maschinelle Lüftung	55 (25 %)
mit maschineller Lüftung	157 (70 %)
keine Angaben	9 (4 %)
ohne Erfassung	61 (27 %)
mit Erfassung	144 (65 %)
keine Angaben	18 (8 %)
Allgemeine Beschreibung: Messungen zu N,N-Dimethylformamid liegen aus 37 Branchen und 71 Arbeitsbereichen vor.	

2.2 Auswertestrategie

- Datenzeitraum 2000 bis 2011
- Standardverfahren im MGU
- Luftproben mit Expositionsbezug
- Arbeitsplatzmessungen
- Probenahme repräsentativ für die Expositionsdauer
- Expositionsdauer ≥ 6 Stunden beziehungsweise < 6 Stunden
- Liegen Analysenergebnisse unterhalb der jeweiligen analytischen Bestimmungsgrenze (a. B.), dann geht der Wert der halben a. B. in die Statistik ein.
- Kollektive mit weniger als zehn Messdaten werden nicht ausgewertet.
- Die Auswertung erfolgt für Branchen- (Kapitel 4) und Arbeitsbereichsgruppen (Kapitel 5).
- Aufgrund der wenigen zur Verfügung stehenden Messwerte erfolgt eine Differenzierung nach
  - stationären Messungen und Messungen an der Person
  - Messwerten mit und ohne Erfassung

  über alle Daten (Abschnitt 6.1).

3 Abkürzungen und Indizes

In den Auswertungstabellen werden folgende Abkürzungen und Indizes verwendet:

Häufigkeit < Werte	Anzahl der Messwerte, die unterhalb der analytischen Bestimmungsgrenze liegen
GW	Grenzwert
a. B.	analytische Bestimmungsgrenze
*	Liegen Analysenergebnisse unterhalb der jeweiligen analytischen Bestimmungsgrenze (a. B.), dann geht der Wert der halben a. B. in die Statistik ein.
+	Der Verteilungswert liegt unterhalb der größten analytischen Bestimmungsgrenze (a. B.) im Datenkollektiv. Die a. B. kann, z. B. in Abhängigkeit von der Probenahmedauer oder dem Volumenstrom, von der in der Einleitung genannten Bestimmungsgrenze abweichen.
!	Die Anzahl der Messwerte unterhalb der analytischen Bestimmungsgrenze (a. B.) ist größer als die Zahl der Messwerte, die durch diesen Summenhäufigkeitswert repräsentiert werden. Daher wird für diesen Summenhäufigkeitswert keine Konzentration angegeben.
**	Es sind weniger als fünf Betriebe im Kollektiv enthalten. Die Daten von weniger als fünf Betrieben sind möglicherweise nicht geeignet, eine gesamte Branche oder einen gesamten Bereich zu repräsentieren. Diese Aussage orientiert sich an REACH Guidance on information requirements and chemical safety assessment. Chapter R.14: Occupational exposure estimation. R.14.4.5: Selection and interpretation of measured data, Inhalation data: "It should be noted that data from one company is unlikely to be representative of a whole industrial sector."

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4 Statistische Auswertungen für Branchengruppen

N,N-Dimethylformamid, Arbeitsplatzmessungen, Datenzeitraum 2000 bis 2011,
Probenahme repräsentativ für Expositionsdauer ≥ 6 h

K.Nr. = Kollektiv-Nummer/ Bezeichnung Branchengruppen	Anzahl Mess-daten	Anzahl Betriebe	Häufig-keit <-Werte Anzahl % *	größte Bestim-mungs-grenze in mg/m³ *	≤ GW %	Konzentrationen in mg/m³		
						50-%-Wert *	90-%-Wert *	95-%-Wert *
K.Nr. 8 keine Einschränkung	163	61	60 36,8	1,3	88,3	+ 0,8	16	32
K.Nr. 61 Kunststoffindustrie, Gummiindustrie	28	15	6 21,4	0,2	92,9	1,2	13	20,2
K.Nr. 74 Kunststofffolien, Herstellung	29	3**	0		72,4	7,5	31,1	34,75
K.Nr. 62 Verarbeiten von flüssigen Beschichtungsstoffen	9	1**	1 11,1	0,3	11,1			
K.Nr. 63 Textilindustrie	51	17	26 51	0,3	100	! a. B.	3,9	4,535
K.Nr. 64 Sonstige Branchen	46	25	27 58,7	1,3	97,8	! a. B	4,28	5,95

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N,N-Dimethylformamid, Arbeitsplatzmessungen, Datenzeitraum 2000 bis 2011,
Probenahme repräsentativ für Expositionsdauer < 6 h

K.Nr. = Kollektiv-Nummer/ Bezeichnung Branchengruppen	Anzahl Mess-daten	Anzahl Betriebe	Häufig-keit <-Werte Anzahl % *	größte Bestim-mungs-grenze in mg/m³ *	≤ GW %	Konzentrationen in mg/m³		
						50-%-Wert *	90-%-Wert *	95-%-Wert *
K.Nr. 9 keine Einschränkung	47	27	21 44,7	2,4	83	+ 1,2	19,27	34,745
K.Nr. 66 Textilindustrie	12	6	4 33,3	0,3	75	2,6	17,76	22,34
K.Nr. 65 Sonstige Branchen	35	21	17 48,6	2,4	85,7	+ 0,95	20	38,25

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5 Statistische Auswertungen für Arbeitsbereichsgruppen

N,N-Dimethylformamid, Arbeitsplatzmessungen, Datenzeitraum 2000 bis 2011,
Probenahme repräsentativ für Expositionsdauer ≥ 6 h

K.Nr. = Kollektiv-Nummer/ Bezeichnung Arbeitsbereichsgruppen	Anzahl Mess-daten	Anzahl Betriebe	Häufig-keit <-Werte Anzahl % *	größte Bestim-mungs-grenze in mg/m³ *	≤ GW %	Konzentrationen in mg/m³		
						50-%-Wert *	90-%-Wert *	95-%-Wert *
K.Nr. 8 **keine Einschränkung**	163	61	60 36,8	1,3	88,3	+ 0,8	16	32
K.Nr. 69 Oberflächenbeschichtung, Spritzen, maschinelles Auftragen	44	13	7 15,9	1,3	77,3	3,8	32,6	46
K.Nr. 68 Kunststoffartikel, Herstellung	14	7	4 28,6	0,2	92,9	1	9	17,3
K.Nr. 67 Spinnerei und Weberei, Nassspinnen	13	4**	10 76,9	0,3	92,3	! a. B.	4,4	14,45
K.Nr. 73 Textilveredelung, Kleben, Beschichten	13	5	6 46,2	0,2	100	+ 0,1	2,7	3,49
K.Nr. 75 Mischen	33	6	0		78,8	6	25,7	33,1
K.Nr. 72 sonstige Arbeitsbereiche	46	32	33 71,7	0,3	100	! a. B.	1,04	2,46

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N,N-Dimethylformamid, Arbeitsplatzmessungen, Datenzeitraum 2000 bis 2011,
Probenahme repräsentativ für Expositionsdauer < 6 h

K.Nr. = Kollektiv-Nummer/ Bezeichnung Arbeitsbereichsgruppen	Anzahl Mess-daten	Anzahl Betriebe	Häufig-keit <-Werte Anzahl % *	größte Bestim-mungs-grenze in mg/m³ *	≤ GW %	Konzentrationen in mg/m³		
						50-%-Wert *	90-%-Wert *	95-%-Wert *
K.Nr. 9 keine Einschränkung	47	27	21 44,7	2,4	83	+ 1,2	19,27	34,745
K.Nr. 81 Oberflächenbeschichtung, Spritzen, maschinelles Auftragen	13	9	2 15,4	2,4	61,5	4,05	35,91	62,8
K.Nr. 82 Sonstige Arbeitsbereiche	34	19	19 55,9	2,4	91,2	! a. B.	13,8	19,2

6 Weitere statistische Auswertungen

6.1 Differenzierung nach Probenahmeart und Erfassung

N,N-Dimethylformamid, Arbeitsplatzmessungen, Datenzeitraum 2000 bis 2011,
Probenahme repräsentativ für Expositionsdauer ≥ 6 h

K.Nr. = Kollektiv-Nummer/ Bezeichnung Probenahmeart Erfassung	Anzahl Mess-daten	Anzahl Betriebe	Häufig-keit <-Werte Anzahl % *	größte Bestim-mungs-grenze in mg/m³ *	≤ GW %	Konzentrationen in mg/m³		
						50-%-Wert *	90-%-Wert *	95-%-Wert *
K.Nr. 24 an der Person ohne Erfassung	12	6	5 41,7	0,3	91,7	0,9	7,8	11,8
K.Nr. 25 an der Person mit Erfassung	52	27	12 23,1	0,3	80,8	4	25,8	34
K.Nr. 26 stationär ohne Erfassung	24	15	14 58,3	0,2	75	! a. B.	39,6	45,6
K.Nr. 27 stationär mit Erfassung	61	27	19 31,1	0,3	96,7	0,6	6	7

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7 Übersichtslisten

7.1 Branchen nach Branchengruppen

N,N-Dimethylformamid, Arbeitsplatzmessungen, Datenzeitraum 2000 bis 2011,
Probenahme repräsentativ für Expositionsdauer ≥ 6 h

Branchengruppen Branche	Anzahl Messwerte
Kunststoffindustrie	**28**
Kunststoff und Kunststoffschaum, Verarbeitung	7
Kunststoffformteile, Herstellung	4
Kunststoffspritzerei	4
Kunststoffplanen, Herstellung	5
Kunststoff und Kunststoffschaum, Herstellung	1
Gummiwaren, Herstellung und Verarbeitung	5
Gummiartikel (technische), Herstellung	2
Verarbeiten von flüssigen Beschichtungsstoffen (Flüssiglackbeschichtung)	**9**
Kunststofffolien, Herstellung	**29**
Textilindustrie	**51**
Schuhherstellung	2
Spinnerei und Weberei	14
Textilveredlung	33
Bekleidungsgewerbe, allgemein	2
Sonstige Branchen	**46**
Biochemische Industrie	1
Anstrichmittel, Herstellung (lösemittelhaltig)	1
Chemiefasern, Herstellung	3
Reibbeläge (Brems- und Kupplungsbeläge), Herstellung, Bearbeitung	1
Porzellan und feinkeramische Massen, Herstellung	4
Flachglas, Herstellung und Verarbeitung	1
Metallbe- und -verarbeitung, allgemein	9
Herstellung von Teilen für Kraftwagen und -motoren (Automobilzulieferung)	2
Elektrotechnik, allgemein	7
Holzbe- und -verarbeitung	2
Großhandel mit Textilien, Bekleidung, Teppichen, Schuhen und Lederwaren	4
Großhandel mit Eisen- und Metallkurzwaren, elektrotechnischen Erzeugnissen, Einrichtungs- und Haushaltsgegenständen, Möbeln, Sportartikeln	1
Einzelhandel (mit Waren verschiedener Art)	3
Kühlhäuser	2
Forschungs- und Untersuchungsinstitute, -labors	1
Museen	1
sonstige Betriebsarten	3
Insgesamt	**163**

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N,N-Dimethylformamid, Arbeitsplatzmessungen, Datenzeitraum 2000 bis 2011,
Probenahme repräsentativ für Expositionsdauer < 6 h

Branchen	Anzahl Messwerte
Sonstige Branchen	35
Chemische Industrie	7
Anstrichmittel, Herstellung (lösemittelhaltig)	2
Kunststoff und Kunststoffschaum, Verarbeitung	2
Kunststoffformteile, Herstellung	1
Kunststoffplanen, Herstellung	3
Gummiartikel (technische), Herstellung	1
Porzellan und feinkeramische Massen, Herstellung	1
Porzellan und Geschirrkeramik, Herstellung	1
Flachglas, Herstellung und Verarbeitung	1
Verarbeiten von flüssigen Beschichtungsstoffen (Flüssiglackbeschichtung)	2
Elektrotechnik, allgemein	3
Polstermöbel, Herstellung	1
Druckerei	1
Großhandel mit Textilien, Bekleidung, Teppichen, Schuhen und Lederwaren	1
Transport, Spedition, Verkehrsbetriebe und dgl.	4
Forschungs- und Untersuchungsinstitute, -labors	3
Gesundheitswesen	1
Textilindustrie	**12**
Spinnerei und Weberei	4
Textilveredlung	8
Insgesamt	**47**

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7.2 Arbeitsbereiche nach Arbeitsbereichsgruppen

N,N-Dimethylformamid, Arbeitsplatzmessungen, Datenzeitraum 2000 bis 2011,
Probenahme repräsentativ für Expositionsdauer ≥ 6 h

Arbeitsbereichsgruppen Arbeitsbereich	Anzahl Messwerte
Spinnerei und Weberei, Nassspinnen	**13**
Kammgarnspinnerei, Aufbereitung, Strecke	1
Halbkamm-, Streichgarnspinnerei, Vliesherstellung, Aufbereitung, Vliesanlage	7
Garnverarbeitung, Seilerei, Zwirnerei und Texturierung, Zwirn-, Fachmaschine	2
Nassspinnen	3
Kunststoffartikel, Herstellung	**14**
Formteileherstellung, Spritzgießen	4
Formteileherstellung, Reaktionsgießen	3
Beschichtungsverfahren, allgemein	4
Nachbearbeitung von Kunststoffartikeln, Schneiden	3
Oberflächenbeschichtung, Spritzen, maschinelles Auftragen	**44**
Oberflächenbeschichtung, Pinseln, Rollen	1
Oberflächenbeschichtung, Tauchen	1
Oberflächenbeschichtung, Spritzen (z. B. mit Druckluft)	10
Oberflächenbeschichtung, maschinelles Auftragen	19
Fertigmachen zum Brand, Spritzen (Farbe oder Glasur) (Keramik)	4
Lackierraum, Spritzwand, Druckluft, manuell (Flüssiglackbeschichtung)	9
Textilveredlung, Kleben, Beschichten	**13**
Druckerei, Kaschieren, Kleben	2
Druckerei, Transferdruckmaschine	3
Chemische Appretur, Beschichtung, sonstiges Appretur- und Beschichtungs-aggregat	2
Chemische Appretur, Beschichtung, Pflatschen	3
Chemische Appretur, Beschichtung, Rakelbeschichtung	3
Mischen	**33**
Mischer, Raum	19
Mischen im Tank	8
Rührbehälter, offen	2
Rohstoffaufbereitung und Ansetzerei, Mischen von Lösungsmitteln	1
Vorbereitung, Mischerei, Aufbereitung	3
Sonstige Arbeitsbereiche	**46**
Heiß-Pressen	4
Platten laminieren	1
Formen schäumen	1
Sonstige Verfahren zum Gießen	1
Trenn- und Bearbeitungsverfahren, Raum	1
Schleifen	1
Stanzen, Schneiden	1
Lagern, Fertigteile, Raum	1
CNC-Bearbeitungsmaschinen	1
Flämmen, Sengen, Brennen	5
Sonstige Bearbeitungsverfahren	4
Abfüllstation, Raum	1
Abwiegen von Hand	1
Reinigen des Materials, durch Abwischen mit Flüssigkeiten	2

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Arbeitsbereichsgruppen Arbeitsbereich	Anzahl Messwerte
Reinigen von Anlagen	1
Technikum, an Einrichtungen	1
Verkaufsraum	2
Labor, Raum	2
Büro	1
Kunststoffschweißen	1
Heißluftschweißen	1
Kleben, sonstige Verfahren	1
Oberflächenbeschichtung, mit Folien, Matten und dgl.	1
Oberflächenbeschichtungsverfahren, sonstige	1
Laserstrahlbohren	1
Presserei, Nachbearbeitung, Heißpresse (Reibbeläge)	1
Montage, Klebstoffauftrag, manuell, lösemittelhaltig (Schuhherstellung)	2
Vulkanisation, Spritzgießpresse (Injection-Moulding) (Gummiwaren, Herstellung und Verarbeitung)	2
Produktion, allgemein (pharmazeutische, biochemische, kosmetische Reinigungs- und Sanitätsprodukte)	1
Umschlagarbeiten, Kommissionieren (Nährmittel und sonstige Gewerbezweige)	2
Insgesamt	**163**

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Deutschen Gesetzlichen Unfallversicherung

N,N-Dimethylformamid, Arbeitsplatzmessungen, Datenzeitraum 2000 bis 2011,
Probenahme repräsentativ für Expositionsdauer < 6 h

Arbeitsbereichsgruppen Arbeitsbereiche	Anzahl Messwerte
Oberflächenbeschichtung, Spritzen, maschinelles Auftragen	**13**
Oberflächenbeschichtung, Pinseln, Rollen	1
Oberflächenbeschichtung, Tauchen	2
Oberflächenbeschichtung, Spritzen (z. B. mit Druckluft)	2
Oberflächenbeschichtung, maschinelles Auftragen	6
Lackierraum, Spritzwand, Druckluft, manuell	1
Werkstatträume, Spritzwand, Druckluft, manuell	1
Sonstige Arbeitsbereiche	**34**
Lagerarbeiten, manuell (z. B. Entladen, Stapeln), allgemein	1
Dissolver, allgemein	2
Flämmen, Sengen, Brennen	2
Abfüllwaage für Fässer, Hobbocks usw.	1
Reinigen des Materials, durch Abwischen mit Flüssigkeiten	1
Reinigen von Anlagen	3
Reinigen von Behältern, maschinell	4
Reparatur und Wartung, in Betrieb	1
Qualitätskontrolle	1
Labor, an Einrichtungen	7
Kunststoffschweißen	1
Heißluftschweißen	1
Kleben, Haftklebstoffe	1
Kleben, sonstige Verfahren	1
Reinigen mit Industriestaubsauger (Keramik)	1
Halbkamm-, Streichgarnspinnerei, Vliesherstellung, sonstige Maschinen (Spinnerei und Weberei)	1
Druckerei, Kaschieren, Kleben (Textilveredlung)	1
Rohstoffaufbereitung und Ansetzerei, Reibwalzen (Herstellung von Klebstoff, Leim, Spachtelmasse, Anstrichmittel, Edelputz, Zement und Bindemittel)	2
Siebreinigen (Druckerei)	1
Formteileherstellung, allgemein (Kunststoffartikel, Herstellung)	1
Insgesamt	**47**

Autorin:

Ulrike Koch
Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA), Sankt Augustin

Annex B3: IFA (2012) MEGA evaluations for the preparation of REACH exposure scenarios for N,N Dimethylformamide (English translation)

Translated by Chemservice S.A.

MEGA evaluations for the preparation of REACH exposure scenarios for N,N Dimethylformamide

1 Introduction

The measured data for workplace exposure evaluated in the following have been gathered and documented in accordance with the principles of the measurement system of the German social accident insurance institutions for exposure assessment (MGU[1] formerly BGMG). The quality of the MGU is upheld by a quality management system that in essence satisfies the requirements of DIN EN ISO 9001. The test laboratories are operated in accordance with DIN EN ISO 17025 "General requirements for the competence of testing and calibration laboratories".

To measure N,N-Dimethylformamide (CAS 68-12-2) exposure at the workplace, two validated methods for the dataperiod (2000 – 2011) were applied:

- Analytical method (2000 – 2007)

A defined volume of air is sucked by a suitable pump through a silica gel tube (type ADS). After extraction using alkaline methanol (methanol with 2 % KOH), the qualitative and quantitative determination is performed by gas chromatography using a nitrogen selective detector (NSD). The quantitative determination is performed in accordance with the internal standard method. The limit of quantification for the standard method of MGU was 0.3 mg/m³ for a sample volume of 40 L at that time.

- Analytical method (2007 – 2011)

A defined volume of air is sucked by a suitable pump through an active coal tube (type B). After extraction using acetone/water in the ratio of 98:2, the qualitative and quantitative determination is performed by gas chromatography using a nitrogen selective detector (NSD). The quantitative determination is performed in accordance with the internal standard method. The limit of quantification for the standard method of MGU amounts to 0.2 mg/m³ for a sample volume of 40 L. Source: MGU-Standard method (2012)

All the surveyed data in the MGU are brought together in the MEGA exposure database (measured data on exposure to hazardous substances at the workplace). The MEGA^{pro} software developed by the IFA (formerly BGIA) makes it possible to statistically analyse the data of the MEGA exposure database on the basis of various selection criteria and evaluation strategies.

[1]Gabriel, S.; Koppisch, D.; Range, D.: The MGU - a monitoring system for the collection and documentation of valid workplace exposure data. Gefahrstoffe – Reinhalt. Luft 70 (2010) No. 1/2, pp. 43-49 http://www.dguv.de/ifa, Webcode d101507

MEGA evaluations: N,N-Dimethylformamide (October 2012)

2 Data situation and evaluation strategy

2.1 Overview of the measured values collected in the MGU, data period 2000 to 2011

N,N-Dimethylformamide (CAS 68-12-2)
Standard method in the MGU
Air samples in relation to exposure

For N,N-Dimethlyformamide, a workplace limit of 15 mg/m³ is given in Germany.

General description	Number of measured values (%)
Total	223
Type of sampling: Stationary	125 (56 %)
Type of sampling: Personal	98 (44 %)
Number of data < quantification limit	92 (41 %)
Number of data > limit value	28 (13 %)
Sampling representative for: Exposure duration ≥ 6 hours Exposure duration ≤ 6 hours	 164 (74 %) 47 (21 %)
Examples: Exposure conditions	
Measuring plan: Measurements at workplaces Measurements indoors	 222 (99.6 %) 1 (0.4 %)
Situation at the firm: disadvantageous	17 (8 %)
Cause for measurements: Occupational disease research	37 (17 %)
Without mechanical ventilation With mechanical ventilation No details	55 (25 %) 157 (70 %) 9 (4 %)
Without recording With recording No details	61 (27 %) 144 (65 %) 18 (8 %)
General description of N,N-Dimethylformamide measurements in 37 branches of industry and 71 work areas	

2.3 Evaluation strategy

-data period 2000 – 2011

-standard methods in the MGU

-air samples in relation to exposure

-workplace measurements

-sampling is representative for the exposure duration

-exposure duration ≥ 6 hours and ≤ 6 hours respectively

-If any single value fell below the measurement method's analytical quantification limit (a.q.), half of each value was adopted in the evaluation.

-Data sets comprising fewer than ten measured data were disregarded.

-The evaluation is performed according to branches of industry (Chapter 4) and for work area groups (Chapter 5).

-Owing to the small number of measured values available, a distinction is made between

-stationary measurements and personal measurements, and

-measured values with and without recording

for all data (Chapter 6.1).

3 Abbreviations and indices

The following abbreviations and indices are used in the evaluation tables:

Frequency < values	Number of measured values below the analytical quantification limit
LV	Limit value
a. q.	Analytical quantification limit (limit of quantification LOQ)
*	If any single values fell below the measurement method's analytical quantification limit (a. q.), half of each value was adopted in the evaluation.
+	The distribution value is below the largest analytical quantification limit in the data set. The quantification limit may deviate from the quantification limit quoted in the introduction, e.g. depending on sampling duration or flow rate.
!	The number of measured values below the analytical quantification limit (a. q.) is greater than the number of measured values represented by this cumulative frequency value. No concentration is therefore given for this cumulative frequency value.
**	There are less than five companies in the data set. The data of less than five companies may probably be not sufficient to represent a complete industry group or range. This statement lies on REACH Guidance on information requirements and chemical safety assessment. Chapter R.14: Occupational exposure estimation. R.14.4.5: Selection and interpretation of measured data, Inhalation data: "It should be noted that data from one company is unlikely to be representative of a whole industry sector."

4. Statistical evaluations for branches of industry

N,N-Dimethylformamide, Workplace measurements, Data period 2000 – 2011, Sampling is representative for exposure duration ≥ 6 hours

D.No. = Data set number / Designation Branch of industry	Number of measured data	Number of firms	Frequency < number of values in %	Largest quantification limit [mg/m³]	≤ limit value %	Concentration [mg/m³]		
						50 percentile	90 percentile	95 percentile
D.No. 8 No limitation	163	61	60 36.8	1.3	88.3	+ 0.8	16	32
D.No. 61 Plastics industry, rubber industry	28	15	6 21.4	0.2	92.9	1.2	13	20.2
D.No. 74 Plastic foil, synthesis	29	3**	0		72.4	7.5	31.1	34.75
D.No. 62 Handling of fluid coating materials	9	1**	1 11.1	0.3	11.1			
D.No. 63 Textile industry	51	17	26 51	0.3	100	! a. q.	3.9	4.535
D.No. 64 Other branches of industry	46	25	27 58.7	1.3	97.8	! a. q.	4.28	5.95

N,N-Dimethylformamide, Workplace measurements, Data period 2000 – 2011, Sampling is representative for exposure duration < 6 hours

D.No. = Data set number / Designation Branch of industry	Number of measured data	Number of firms	Frequency < number of values in %	Largest quantification limit [mg/m³]	≤ limit value %	Concentration [mg/m³]		
						50 percentile	90 percentile	95 percentile
D. No. 9 No limitations	47	27	21 44.7	2.4	83	+ 1.2	19.27	34.745
D.No. 66 Textile industry	12	6	4 33.3	0.3	75	2.6	17.76	22.34
D.No. 65 Other branches of industry	35	21	17 48.6	2.4	85.7	+ 0.95	20	38.25

5. Statistical evaluation for work area groups

N,N-Dimethylformamide, Workplace measurements, Data period 2000 – 2011, Sampling is representative for exposure duration ≥ 6 hours

D.No. = Data set number / Designation Work area groups	Number of measured data	Number of firms	Frequency < number of values in %	Largest quantification limit [mg/m³]	≤ limit value %	Concentration [mg/m³]		
						50 percentile	90 percentile	95 percentile
D.No. 8 No limitations	163	61	60 36.8	1.3	88.3	+ 0.8	16	32
D.No. 69 Surface coating, spraying, mechanical coating	44	13	7 15.9	1.3	77.3	3.8	32.6	46
D.No. 68 Plastic articles, synthesis	14	7	4 28.6	0.2	92.9	1	9	17.3
D.No. 67 Spinning, weaving, wet spinning	13	4**	10 76.9	0.3	92.3	! a.q.	4.4	14.45
D.No. 73 Textile finishing, glueing, coating	13	5	6 46.2	0.2	100	+ 0.1	2.7	3.49
D.No. 75 Mixing	33	6	0		78.8	6	25.7	33.1
D.No. 72 Other work area groups	46	32	33 71.7	0.3	100	! a.q.	1.04	2.46

N,N-Dimethylformamide, Workplace measurements, Data period 2000 – 2011, Sampling is representative for exposure duration < 6 hours

D.No. = Data set number / Designation Work area groups	Number of measured data	Number of firms	Frequency < number of values in %	Largest quantification limit [mg/m³]	≤ limit value %	Concentration [mg/m³]		
						50 percentile	90 percentile	95 percentile
D.No. 9 No limitations	47	27	21 44.7	2.4	83	+ 1.2	19.27	34.745
D.No. 81 Surface coating, spraying, mechanical coating	13	9	2 15.4	2.4	61.5	4.05	35.91	62.8
D.No. 82 Other work area groups	34	19	19 55.9	2.4	91.2	! a.q.	13.8	19.2

6. Further statistical evaluations

6.1 Differentiation according to mode of sampling and recording

N,N-Dimethylformamide, Workplace measurements, Data period 2000 – 2011, Sampling is representative for exposure duration ≥ 6 hours

D.No. = Data set number / Designation Work area groups	Number of measured data	Number of firms	Frequency < number of values in %	Largest quantification limit [mg/m³]	≤ limit value %	Concentration [mg/m³]		
						50 percentile	90 percentile	95 percentile
D.No. 24 personal without recording	12	6	5 41.7	0.3	91.7	0.9	7.8	11.8
D.No. 25 personal with recording	52	27	12 23.1	0.3	80.8	4	25.8	34
D.No. 26 stationary without recording	24	15	14 58.3	0.2	75	! a.q.	39.6	45.6
D.No. 27 stationary with recording	61	27	19 31.1	0.3	96.7	0.6	6	7

7. Overview lists

7.1 Branch of industry according to branch of industry group

N,N-Dimethylformamide, Workplace measurements, Data period 2000 – 2011, Sampling is representative for exposure duration ≥ 6 hours

Branch of industry group Branch of industry	Number of measured values
Plastics industry	**28**
Plastic and plastic foam, processing	7
Plastic moulded parts	4
Plastics injection moulding	4
Plastic tarpaulins, synthesis	5
Plastic and plastic foam, synthesis	1
Rubber products, synthesis and processing	5
Rubber articles (techn.), synthesis	2
Processing of fluid coating materials (Liquid paint applications)	**9**
Plastic foil, synthesis	**29**
Textile industry	**51**
Manufacture of shoes	2
Spinning and weaving	14
Textile finishing	33

Textile products, in general	2
Other branches of industry	**46**
Biochemical industry	1
Manufacture of paints (solvent-rich)	1
Manufacture of chemical fibres	3
Manufacture and processing of friction linings (break linings and clutch facings)	1
Manufacture of porcelain and fine ceramic materials	4
Manufacture and processing of flat glass	1
Metal working and metal processing, in general	9
Manufacture of components for motor vehicles and engines (automotive supply sector)	2 7
Electrical engineering, general	2
Wood working and wood processing	4
Wholesale trade with textiles, clothing, carpets, shoes and leather products	
Wholesale trade with iron and metal short parts, electrical articles, furniture, household articles, sports items	1 3
Retail trade (with different products)	2
Cold storage houses	1
Research and testing institutes and laboratories	1
Museums	3
Others	
Total	**163**

N,N-Dimethylformamide, Workplace measurements, Data period 2000 – 2011, Sampling is representative for exposure duration < 6 hours

Branch of industry	**Number of measured values**
Other branches of industry	**35**
Chemical industry	7
Manufacture of paints (solvent-rich)	2
Processing of plastic and plastic foam	2
Manufacture of plastic molded parts	1
Manufacture of plastic tarpaulins	3
Manufacture of rubber products (techn.)	1
Manufacture of porcelain and fine ceramic materials	1
Manufacture of porcelain and ceramic crockery	1
Manufacture and processing of flat glas	1
Processing of fluid coating materials (Liquid paint applications)	2
Electrical engineering, general	3
Manufacture of upholstered furniture	1
Print shop	1
Wholesale trade with textiles, clothing, carpets, shoes and leather products	1
Transport, forwarding, public transport companies and such	4
Research and testing institutes and laboratories	3
Healthcare	1
Textile industry	**12**
Spinning and weaving	4
Textile finishing	8
Total	**47**

7.2 Work areas according to work area group

N,N-Dimethylformamide, Workplace measurements, Data period 2000 – 2011, Sampling is representative for exposure duration ≥ 6 hours

Work area groups **Work area**	**Number of measured values**
Spinning, weaving, wet spinning	**13**
worsted yarn spinning, preparation, production line	1
Half worsted spinning, woollen yarn spinning, manufacture of fleece, preparation, non woven installation	7
Yarn processing, rope manufacture, spinning mill and texturing, twisting and specialized machinery	2
Wet spinning	3
Manufacture of plastic articles	**14**
Manufacture of moulded parts, injection moulding	4
Manufacture of moulded parts, reaction-casting	3
Coating process, general	4
Finishing of plastic articles, cutting	3
Surface coating, spraying, mechanical coating	**44**
Surface coating, spraying, brushing	1
Surface coating, dipping	1
Surface coating, spraying (i.e. with pressurised air)	10
Surface coating, mechanical coating	19
Finishing for burning, spraying (paint and glaze) (ceramics)	4
Lacquering rooms, spraying area, pressurised air, manual (liquid painting)	9
Textile finishing, glueing, coating	**13**
Printing, laminating, glueing	2
Printing, printing press	3
Chemical finishing, coating, other finishing and coating materials	2
Chemical finishing, coating, padding	3
Chemical finishing, coating, blanket coating	3
Mixing	**33**
Mixers, room	19
Mixing in tanks	8
Stirring tank, open system	2
Processing of raw materials and process preparation, mixing of solvents	1
Preparation, mixing, processing	3
Work areas, miscellaneous	**46**
Hot pressing	4
Laminating of sheets	1
Foam injection	1
Casting, other methods	1
Separation and treatment processes, room	1
Grinding	1
Punching, cutting	1
Storage, prefabricated materials, room	1
CNC processing machine	1
Flaming, singeing, burning	5
Other processing methids	4
Filling station, room	1
Weighing, manual	1
Cleaning of materials due to wiping with liquids	2

Cleaning of equipment	1
Technical center, equipment	1
Sales room	2
Laboratory, room	2
Office	1
Plastics welding	1
Welding with hot air	1
Glueing, other methods	1
Surface coating, with foils, mats and such	1
Surface coating, other methods	1
Laser drilling	1
Pressing, post-processing, hot pressing (friction linings)	1
Installation, adhesive application, manual, solvent-rich (manufacture of shoes)	2
Vulcanisation, injection moulding (rubber products, manufacture and processing)	2
Production, general (pharmaceutical, biochemical, cosmetic cleaning and sanitary products)	1
Cargo handling, order picking (nutriment and other branches of industry)	2
Total	**163**

N,N-Dimethylformamide, Workplace measurements, Data period 2000 – 2011, Sampling is representative for exposure duration < 6 hours

Work area groups **Work area**	**Number of measured values**
Surface coating, spraying, mechanical coating	**13**
Surface coating, brushing, rolling	1
Surface coating, dipping	2
Surface coating, spraying (i.e. with pressurised air)	2
Surface coating, mechanical coating	6
Lacquering rooms, spraying area, pressurised air, manual	1
Workshops, spraying area, pressurised air, manual	1
Work areas, miscellaneous	34
Warehouse operations, manual (i.e. unloading, stacking), general	1
Dissolver, general	2
Flaming, singeing, burning	2
Filling scale for barrels, hobbocks, etc.	1
Cleaning of materials due to wiping with liquids	1
Cleaning of equipment	3
Cleaning of vessels, mechanical	4
Repair and maintenance, in operation	1
Quality control	1
Laboratory, in institutions	7
Plastics welding	1
Welding with hot air	1
Glueing, adhesives	1
Glueing, other methods	1
Cleaning with industrial vacuum cleaner (ceramics)	1
Half worsted spinning, woollen yarn spinning, manufacture of fleece, other machines (spinnery and weavery)	1
Printing, laminating, glueing (textile finishing)	1
Processing of raw materials and process preparation, distributor rollers (Manufacture of glue, paste, filler, coating, fining coat, cement and binder)	2

Sieve cleaning (print shop) Manufacture of moulded parts, general (plastic articles, manufacture)	1 1
Total	**47**

Author:

Ulrike Koch
Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA), Sankt Augustin

Annex B4: Statement by BG ETEM on MEGA-evauluations for dimethylformamide

BG ETEM
Energie Textil Elektro
Medienerzeugnisse

Präventionsabteilung
Fachgebiet Gefahrstoffe
Messtechnischer Dienst

BG ETEM • Postfach 51 05 80 • 50941 Köln

Industrievereinigung Chemiefasern
Herr Rauch

Ihr Zeichen:
Ihre Nachricht vom:
Unser Zeichen:
(bitte stets angeben)
Ihr/e Ansprechpartner/in: **Dirk Fendler**
Telefon: 0221 3778-6123
Telefax: 0221 3778-6131
E-Mail: Fendler.dirk@bgetem.de

Datum: 12.08.2014

Erläuterungen zur Gefahrstoffmessung 10-0975/2007 auf Dimethylformamid

Sehr geehrter Herr Rauch,

wie angefragt im Folgenden einige Erläuterungen zu unserer Vorgehensweise bei der Durchführung von Gefahrstoffmessungen:

Generell führt der Messtechnische Dienst der BG ETEM Gefahrstoffmessungen im Rahmen der Prävention durch. Die größte Anzahl der Messungen erfolgt dabei durch Messanforderungen unserer technischen Aufsichtsbeamten um z.B. festzustellen, ob Arbeitsplatzgrenzwerte eingehalten werden. Je nach Fragestellung wird dabei eine angepasste Messstrategie angewendet. Die Messergebnisse werden dem Mitgliedsbetrieb in Form eines Messberichtes zur Verfügung gestellt. Ggf. wird der Mitgliedsbetrieb zur Umsetzung weiterer Schutzmaßnahmen beraten.

Die Messergebnisse sowie alle relevanten Randbedingungen zu unseren Messungen werden in der MEGA-Datenbank abgelegt und können durch die Unfallversicherungsträger ausgewertet werden.

Bei dem von Ihnen angesprochenen Vorgang 10-0975/2007 handelt es sich um eine Arbeitsplatzmessung an einer Nassspinnanlage von Polyacrylnitrilfasern mittels Dimethylformamid (DMF) aus dem Jahre 2008 in einem Forschungsinstitut, welches bei der BG ETEM versichert ist. Die Anlage, an der die Messungen erfolgten, wurde zu Versuchszwecken aufgebaut. Während des Betriebes der Anlage wurde die Exposition des Anlagenbedieners durch eine personengetragene Messung ermittelt. Parallel zu der personengetragenen Messung erfolgten zusätzlich stationäre Messungen unmittelbar an den Bädern (Emissionsquellen) bzw. zwischen den Bädern. Während das Messergebnis der personengetragenen Messung am Bediener mit einem Messwert von

Berufsgenossenschaft
Energie Textil Elektro Medienerzeugnisse
Gesetzliche Unfallversicherung
Körperschaft des öffentlichen Rechts

Gustav-Heinemann-Ufer 130
50968 Köln
Telefon 0221 3778-0
Telefax 0221 3778-1199
E-Mail info@bgetem.de

Commerzbank Köln
Bankleitzahl 370 400 44
Konto-Nr. 110 015 500
IBAN DE55 37040044011001550O
BIC COBADEFF370

IK- Nr.: 12 0590446

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5 mg/m³ deutlich unter dem damaligen Arbeitsplatzgrenzwert von 30 mg/m³ lag, wurde direkt über dem Fällbad mit 32 mg/m³ erwartungsgemäß ein deutlich höherer Wert ermittelt. Zwischen den Bädern wurde ein Messwert von 3 mg/m³ ermittelt.

Die Messergebnisse wurden dem Mitgliedsbetrieb in Form eines Messberichtes zur Verfügung gestellt.

Für weitere Fragen stehe ich gerne zur Verfügung.

Mit freundlichen Grüßen
Im Auftrag

Dirk Fendler
Leiter des Messtechnischen Dienstes
BG ETEM

Annex B5: SGS (2013a) Determination of DMF in Leather cuttings and PU cuttings.

Confidential information

Annex B6: SGS (2013b) Determination of DMF in Leather cuttings and PU cuttings.

Confidential information

Annex B7: Migration tests of DMF in fiber material (DIN EN ISO 6330)

Confidential information.

Appendices Section F

Annex F1: General SEA Framework

Data sources

Two sources of information were used for conducting the SEA: responses to the questionnaire, which is presented in Annex 2 and Eurostat. The questionnaire was used to collect the information regarding the use of DMF and possible reactions to analysed restrictions. The data from the Structural Business Statistics of Eurostat were also used. More precisely, data were taken from the Annual detailed enterprise statistics for industry (NACE Rev. 2, B-E) as the new activity classification (NACE Rev 2) allows for identifying very close sectors to the ones studied. The table below presents the NACE codes and labels corresponding to the analysed industries.

Table F34. NACE codes used in the SEAH

Industry	NACE code	Label
Fiber	C2060	Manufacture of man-made fibres
Industrial gases	C2011	Manufacture of industrial gases
Textile-polyurethane	C1330	Finishing of textile

The Eurostat data were used only when essential information concerning the industry's situation was not available in the questionnaires. Concretely, the ratio of personnel cost to turnover was taken from this source for all the industries and the ratio of gross operating surplus to turnover was used in the case of the fibre industry as information on the operating margin was not available from the questionnaire.

Analysed reactions

The collected data allowed to analyse six RMOs (a complete restriction, three types of partial restrictions, a targeted restriction and the authorisation) detailed in the questionnaire presented in Annex 2. For each RMO, the following reactions were considered:

- Business termination
- Business relocation
- Use of an alternative substance (substitution)

Direct impacts

Analysed direct impacts are presented in the following table and explained below.

Table F35. Analysed direct impacts

Type of reaction	Lost margin	Additional fixed cost	Additional variable cost
Business termination	X	X	
Business relocation		X	
Substitution	X[3]	X	X

[3] Lost margin for the period preceding the implementation of an alternative for DMF is only considered for industrial gases.

Business termination

As indicated in the following table, different types of direct impacts were evaluated for different types of reactions. In case of business termination, direct economic impacts concern lost margin in the EEA and additional fixed costs (for example capital destruction). Lost margin is estimated by using information about turnover and margin present on the questionnaire. On a first step, an annual estimation of the turnover was made in a 15 years horizon. For this purpose were used: the turnover and margin for products produced in the EEU using DMF declared for 2013 (question 8 of the questionnaire), the market growth rate projected for the following three years (question 11) and the market trend expected by firms (calculations based on questions 10 and 11). Subsequently, by applying the ratio margin/turnover[4] to each year's DMF turnover the annual lost margin was calculated. The net present value of these lost flows was calculated using a 4% discount rate.

Business termination fixed costs are taken into account when provided explicitly by respondents (question 17 in the questionnaire). Closing costs are taken as a one shot cost incurred on the first year the RMO comes into effect.

Business reallocation

In case of business relocation, a conservative assumption is made that business relocation would not have any negative impact on total turnover and/or variable costs. The gross operating margin is assumed to be kept in Europe despite relocation of the productive activities. Additional fixed costs are assumed to be at the same level as business termination costs when the latter are available and are equally accounted for as one shot costs.

Substitution

In case of the substitution, direct economic impacts are related to additional fixed costs (for example process adaptation costs) and additional variable costs (for example additional production costs, additional administrative costs and substances and reformulation costs). Additional fixed and variable costs were taken into account using responses to questions 26 to 28 on the questionnaire. Specific details on the estimation for each industry are discussed in sections concerning specific industries.

Indirect impacts

As described in the table below, two types of indirect impacts are considered: lost jobs and lost profits of DMF producers.

Table F36. Analysed indirect impacts

Type of reaction	Lost jobs	Lost profits of DMF producers
Business termination	X	X
Business relocation	X	X
Substitution		X

Lost jobs

Indirect impacts concern lost jobs in case termination or relocation. Their assessment takes two forms. First, the number of lost job is assessed using the information from questions 39 to 41 of the questionnaire. When this information was not available, the number of job lost was estimated by using

[4] Information on the margin was not available for the fibre industry. Therefore, this ratio was estimated by using gross operating surplus and turnover from Eurostat's Structural Business Statistics corresponding industry.

the total number of employees in the EAA (question 3 of the questionnaire) and the ratio of total turnover (question 2) to DMF turnover (questions 8).

Second, lost jobs were expressed in monetary terms. The estimation was made by first applying to annual turnover the ratio of personnel cost to turnover, taken from Eurostat. Next, the obtained amount was divided by the number of employees. Finally, it was multiplied by the number of estimated lost jobs.

Lost profits of DMF producers

A wider impact regarding the profit loss on DMF lost sales upstream was considered in the assessment of the economic costs related to a RMO. These were estimated for each industry in two steps. First, the value of DMF purchases was identified for the industry. Second, the identified value was multiplied by the margin of upstream suppliers. As this margin was not available directly from questionnaires responses, a margin of 9.4% was assumed, which according to the Eurostat constitutes the ratio of gross operating surplus to turnover for the manufacture of chemicals and chemical products industry[5].

Time horizon
All the impacts were estimated using a time horizon of 15 years and a discount rate of 4%. Fixed costs are considered to take place in the first year. Recurrent costs are considered to take place every year during the analysed period when they are given as a percentage of turnover. When given as o total amount for the entire period, they are treated as fixed costs, meaning that they are considered to take place on the first year once for all.

Data aggregation
Data aggregation was necessary for the textile industry. Industry level parameters were determined either by summation, as it is the case for example of industry turnover and the number of jobs lost, or either through the mean of individual responses, as it is the case of the expected market growth rate.

Some firms did not provide complete answers to the questionnaire. In order to complete the missing information, the mean value from responding firms for a given post was applied to non-responding firms. Further details on specific parameters and aggregation are given in section F.5.4.

Data extrapolation
The information given by the questionnaires only allows for assessing the economic impacts on a part of the market. It does not provide information for firms not responding to the questionnaire. In order to generalize the estimated impacts for a given industry, responding firms are taken as a bench mark and their estimated impacts are extrapolated to the market according to the relationship between their own estimates of the total market size and their stated sizes.

Compliance costs
Compliance costs are negligible in the case of partial restrictions and most of the industries members declare to operate already under very restrictive norms. Additionally, the part of the firms who would continue to operate by modifying significantly their exposition is very small. However, compliance costs are significant in the case of firms operating under authorization or undertaking a substitution process. Despite this fact, there is no information available about these costs allowing for quantifying them. Therefore, compliance costs are not integrated into this impact assessment.

[5] This ratio corresponds to the ratio gross operating surplus/turnover for the European Union (28 countries) in 2011. Available at Eurostat, Structural Business Statistics, Annual detailed entreprise statistics fort he industry (NACE Rev. 2, B-E). Manufacture of chemicals and chemical products (NACE code C20). epp.eurostat.ec.europa.eu/portal/page/portal/european_business/data/database

Specific information regarding the methodology for industrial gases

[Confidential information]

Specific information regarding the methodology for fibers

[Confidential information]

Specific information regarding the methodology for coating textiles

[Confidential information]

Annex F2: SEA - Questionnaire

27 June, 2014

FINAL
Questionnaire for the Socio-Economic Analysis (SEA) of N,N-Dimethylformamide (in the following DMF) CAS-No.: 68-12-2

Remark: *Please always indicate whether your answers are:*

- *Public: e.g. may be cited as "one company…." Or "association XY claims for their sector …."*
- *Confidential information: e.g. for consolidation (consolidated data will be public). Confidential data of a single company will only be visible to dossier submitter and the Rapporteur only, but not to other RAC and SEAC members.*

1. Company/Association description

1 Please indicate the industry that you are representing

Pharmaceutical industry	Industrial gases industry	Agrochemicals	Textiles/ polyurethanes	Fibers	Other (please specify)

2 Please indicate your turnover (in €) in 2013

Turnover generated in the EU on products produced in the EU	Turnover generated in the EU on imported products	Worldwide turnover

3 Please indicate the number of employees in 2013 in the EEA area

In the EEA	Outside the EEA

4 Please indicate any other general information about your company that you consider relevant for the socio-economic analysis of DMF.

2. Use of DMF

5 Please explain how and for what purposes you use DMF

6 Please indicate the volume and the value (in €) of DMF that you used in 2013 in the EU-EEA and outside the EU-EEA

	Volume	Value (in €)
In the EEA		
Outside the EEA		

7 Please indicate the number of your employees exposed to DMF in 2013

In the EEA	Outside the EEA
8	9

10 Please indicate your turnover and your margin (in €) for products produced in the EEU using DMF and imported products containing DMF in the EEU in 2013.

	Turnover (in €)	Margin (in €)
Products produced in the EEA using DMF		
Imported products containing DMF		

11 Please provide your estimate of the total market size (in €) for products produced in the EEA using DMF and imported products containing DMF in the EEA in 2013.

Products produced in the EU using DMF	Imported products containing DMF

12 Please indicate whether the market trend for your use of DMF is downward, stabilizing or upward.

Downward	Stabilizing	Upward	Unknown

13 Please indicate your estimate of the growth rate of the market for your use of DMF in the next three years.

2014	2015	2016

14 Please provide your estimate of the number of SMEs concerned by a potential DMF restriction and their combined market share in 2013.

	SMEs producing products using DMF in the EEA	SMEs importing products containing DMF to the EEA
Number		
Market share (in turnover)		

15 Please indicate any other information regarding your use of DMF that you consider relevant for the socio-economic analysis of DMF.

3. Direct impacts

3.1. Considered scenarios

For the following questions, please consider the following scenarios.

Complete restriction	Total Ban of DMF in the EEA
Partial restriction 1	• DMF shall not be manufactured and used by professional or industrial workers, unless: - the 8-hour TWA exposure will remain below 15 mg/m^3 and the 15 min peak exposure (STEL) remains below 30 mg/m^3; - dermal exposure is avoided by preventative measures to comply with the DNELs for dermal exposure; - the professional use is restricted to professional laboratories only. • Articles may not be placed on the market if they or parts thereof, contain DMF in concentrations higher than **0.1%** by mass (w/w). The concentration limit should be applicable for each individual part of the article.
Partial	• DMF shall not be manufactured and used by professional or industrial workers, unless:

restriction 2	- the 8-hour TWA exposure will remain below 15 mg/m^3 and the 15 min peak exposure (STEL) remains below 30 mg/m^3; - dermal exposure is avoided by preventative measures to comply with the DNELs for dermal exposure; - the professional use is restricted to professional laboratories only. • Articles may not be placed on the market if they or parts thereof, contain DMF in concentrations higher than **0.3%** by mass (w/w). The concentration limit should be applicable for each individual part of the article.
Partial restriction 3	• DMF shall not be manufactured and used by professional or industrial workers, unless: - the 8-hour TWA exposure will remain below 15 mg/m^3 and the 15 min peak exposure (STEL) remains below 30 mg/m^3; - dermal exposure is avoided by preventative measures to comply with the DNELs for dermal exposure; - the professional use is restricted to professional laboratories only. • Articles may not be placed on the market if they or parts thereof, contain DMF in concentrations higher than **1.5%** by mass (w/w). The concentration limit should be applicable for each individual part of the article.
Targeted restriction	Targeted Restriction: for the uses/mixtures/articles for which alternatives appear to be readily available, the use of DMF is banned (e.g. paints; glue, paint stripper; spraying; hand mixing etc.)
Authorisation	Total ban of DMF, except if firms will submit an authorisation dossier or for uses exempt from authorisation.

3.2. Business termination

16 For each scenario, please indicate whether you think that the restriction would force you to close at least part of your business.

	Complete restriction	**Partial restriction 1**	**Partial restriction 2**	**Partial restriction 3**	**Targeted restriction**	**Authorisation**
Yes						
No						

17 If you have answered yes at least once in question 14, please estimate which part (in %) of your business deriving from products using or containing DMF in the EU you will be forced to terminate in each scenario. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	**Reaction type**	**Worst case**	**Most-likely case**	**Best case**
Complete	Immediate			
	In 2-3 years			
Partial 1	Immediate			
	In 2-3 years			
Partial 2	Immediate			
	In 2-3 years			
Partial 3	Immediate			
	In 2-3 years			
Targeted	Immediate			
	In 2-3 years			
Authorisation	Immediate			
	In 2-3 years			

18 If you have answered yes at least once in question 14, please indicate the minimum time you require for the restriction. Please indicate "if" and "why" you may require a longer adaptation period for proportionality reasons.

	Complete	**Partial**	**Partial**	**Partial**	**Targeted**	**Authorisation**

	restriction	restriction 1	restriction 2	restriction 3	restriction	
Minimum time required						
Longer adaptation period required (yes/no)						
Reasons for longer adaptation period						

19 If you have answered yes at least once in question 14, please estimate your additional costs (in €, if any) that you would incur because of the termination of manufacturing of products using DMF in the EU and/or importing products containing DMF to the EU (for example capital destruction). Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Worst case	Most-likely case	Best case
Complete	Immediate			
	In 2-3 years			
Partial 1	Immediate			
	In 2-3 years			
Partial 2	Immediate			
	In 2-3 years			
Partial 3	Immediate			
	In 2-3 years			
Targeted	Immediate			
	In 2-3 years			
Authorisation	Immediate			
	In 2-3 years			

20 Please specify costs considered in question 17.

3.3. Business relocation

21 For each scenario, please indicate whether you think that the restriction would force you to relocate your business outside the EEA.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation
Yes						
No						

22 If you have answered yes at least once in question 19, please estimate which part (in %) of your business derived from manufacturing products using DMF in the EU you will be forced to reallocate outside the EU. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Worst case	Most-likely case	Best case
Complete	Immediate			

	In 2-3 years			
Partial 1	Immediate			
	In 2-3 years			
Partial 2	Immediate			
	In 2-3 years			
Partial 3	Immediate			
	In 2-3 years			
Targeted	Immediate			
	In 2-3 years			
Authorisation	Immediate			
	In 2-3 years			

3.4. Use of an alternative substance

23 For each scenario, please indicate whether you think that the restriction would force you to use an alternative substance.

	Complete restriction[6]	**Partial restriction 1**	**Partial restriction 2**	**Partial restriction 3**	**Targeted restriction**	**Authorization**
Yes						
No						

24 If you have answered yes at least once in question 21, please indicate an alternative substance that you would consider (you may indicate more than one substance).

	Complete restriction	**Partial restriction 1**	**Partial restriction 2**	**Partial restriction 3**	**Targeted restriction**	**Authorisation**
NMP (CAS 872-50-4)						
DMAC CAS 127-19-5						
DMSO (CAS 67-68-5)						
Other (please specify)						
Other (please specify)						
Other (please specify)						

25 If you have answered yes at least once in question 21, please indicate whether you have already experience with using the indicated alternative substance and if so, how would you evaluate it as an alternative to DMF for your industry.

Substance	**Your experience with using the substance**		**General assessment of the experience**
	Yes	**No**	

[6] Please note that a complete restriction does not require the use of an alternative substance if you opt for the business closure of business relocation.

NMP (CAS 872-50-4)			
DMAC CAS 127-19-5			
DMSO (CAS 67-68-5)			
Other (please specify)			
Other (please specify)			
Other (please specify)			

26 If you have answered yes at least once in question 21, please indicate whether to your best knowledge the alternative substance has been already applied for your use (not necessarily by you) and if so how would you evaluate it as an alternative for DMF for your industry.

Substance	**Industry experience with using the substance**		**General assessment of the experience**
	Yes	**No**	
NMP (CAS 872-50-4)			
DMAC CAS 127-19-5			
DMSO (CAS 67-68-5)			
Other (please specify)			
Other (please specify)			
Other (please specify)			

27 Please indicate how much time the industry would need to implement each alternative.

Substance	**Required time**
NMP (CAS 872-50-4)	
DMAC CAS 127-19-5	
DMSO (CAS 67-68-5)	
Other (please specify)	
Other (please specify)	
Other (please specify)	

28 If you have answered yes at least once in question 21, please estimate by how much (in €) you expect your fixed costs (for example process adaptation costs) and variable costs (for example additional production costs, additional administrative costs and substances and reformulation costs) would increase as a result of the substitution of DMF by an alternative substance.

Please consider two time horizons: your immediate reaction and your reaction in 2-3 years.

Please consider three cases: worst case, most-likely case and best case.

Restriction	**Reaction type**	**Cost type**	**Worst case**	**Most-likely case**	**Best case**
Complete	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Partial 1	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			

		Variable cost			
Partial 2	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Partial 3	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Targeted	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Authorisation	Immediate	Fixed cost			
	In 2-3 years	Variable cost			

29 Please specify fixed costs considered in question 26.

30 Please specify variable costs considered in question 26.

3.5. Continued use of DMF

31 For each scenario, please indicate whether you think that you will continue using DMF.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation
Yes						
No						

3.6. DMF Exposure reduction

32 If you have answered yes at least once in question 29, lease indicate whether you think that the restriction would force you to reduce the exposure to DMF.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation
Yes						
No						

33 If you have answered yes at least once in question 30, please estimate by how much (in €) you expect your fixed costs (for example process adaptation costs) and variable costs (for example additional production costs, additional administrative costs, additional exposure testing and costs of monitoring program) would increase as a result of the reduction of DMF exposure. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Cost type	Worst case	Most-likely case	Best case
Complete	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			

		Variable cost			
Partial 1	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Partial 2	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Partial 3	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Targeted	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Authorisation	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			

34 Please specify fixed costs considered in question 31.

35 Please specify variable costs considered in question 31.

3.6.1. Reduction of DMF impurities in articles

36 If you have answered yes at least once in question 29, please indicate whether you think that the restriction would force you to reduce DMF impurities in products.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorizstion
Yes						
No						

37 If you have answered yes at least once in question 34, please estimate by how much (in €) you expect your fixed costs (for example process adaptation costs) and variable costs (for example additional production costs, additional administrative costs, additional costs of monitoring program) would increase as a result of the reduction of DMF impurities in products. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Cost type	Worst case	Most-likely case	Best case
Complete	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Partial 1	Immediate	Fixed cost			
		Variable cost			

	In 2-3 years	Fixed cost			
		Variable cost			
Partial 2	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Partial 3	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Targeted	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Authorisation	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			

38 Please specify fixed costs considered in question 35.

39 Please specify variable costs considered in question 35.

3.7. Other effects

40 Please indicate any other information regarding direct impacts of considered restriction scenarios that you consider relevant for the socio-economic analysis of DMF.

4. Indirect impacts

4.1. Effects on employment

41 For each scenario, please indicate whether you think that the restriction would force you to change the number of employees in the EU.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation
Yes						
No						

42 If you have answered yes at least once in question 39, please estimate by how many the number of your employees will change in the EU. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Worst case	Most-likely case	Best case
Complete	Immediate			
	In 2-3 years			
Partial 1	Immediate			
	In 2-3 years			

Partial 2	Immediate			
	In 2-3 years			
Partial 3	Immediate			
	In 2-3 years			
Targeted	Immediate			
	In 2-3 years			
Authorisation	Immediate			
	In 2-3 years			

43 Please specify types of employees considered in question 40.

44 For each scenario, please indicate whether you think that the restriction would force you to change the number of employees outside the EEA.

	Complete restriction	**Partial restriction 1**	**Partial restriction 2**	**Partial restriction 3**	**Targeted restriction**	**Authorisation**
Yes						
No						

45 If you have answered yes at least once in question 42, please estimate by how many the number of your employees will change outside the EEA. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	**Reaction type**	**Worst case**	**Most-likely case**	**Best case**
Complete	Immediate			
	In 2-3 years			
Partial 1	Immediate			
	In 2-3 years			
Partial 2	Immediate			
	In 2-3 years			
Partial 3	Immediate			
	In 2-3 years			
Targeted	Immediate			
	In 2-3 years			
Authorization	Immediate			
	In 2-3 years			

46 Please specify types of employees considered in question 43.

4.2. Price change

47 For each scenario, please indicate whether you think that the restriction would force you to increase you prices in the EEA.

	Complete restriction	**Partial restriction 1**	**Partial restriction 2**	**Partial restriction 3**	**Targeted restriction**	**Authorisation**
Yes						
No						

48 If you have answered yes at least once in question 45, please estimate by how much (in %) your prices would increase in the EU. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Worst case	Most-likely case	Best case
Complete	Immediate			
	In 2-3 years			
Partial 1	Immediate			
	In 2-3 years			
Partial 2	Immediate			
	In 2-3 years			
Partial 3	Immediate			
	In 2-3 years			
Targeted	Immediate			
	In 2-3 years			
Authorisation	Immediate			
	In 2-3 years			

49 If you have answered yes at least once in question 45, please indicate reasons why you believe that your price could change in different restriction scenarios.

Restriction	Reasons
Complete	
Partial 1	
Partial 2	
Partial 3	
Targeted	
Authorisation	

4.3. Lost business as a result of the price increase

50 If you have answered yes at least once in question 45, please indicate whether you think that the price increase would lead to business loss.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation
Yes						
No						

51 If you have answered yes at least once in question 48, please estimate by how much (in %) business derived from manufacturing products using DMF and importing products containing DMF in the EU you think you would lose. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Worst case	Most-likely case	Best case
Complete	Immediate			
	In 2-3 years			
Partial 1	Immediate			
	In 2-3 years			
Partial 2	Immediate			
	In 2-3 years			

Partial 3	Immediate			
	In 2-3 years			
Targeted	Immediate			
	In 2-3 years			
Authorisation	Immediate			
	In 2-3 years			

52 If you have answered yes at least once in question 48, please indicate to what extent in your opinion your lost business would be taken over by companies located outside the EU.

Restriction	Likely consequences
Complete	
Partial 1	
Partial 2	
Partial 3	
Targeted	
Authorisation	

4.4. Effects on SMEs

53 For each scenario, please indicate how in your opinion SMEs would be affected.

Restriction	Likely consequences
Complete	
Partial 1	
Partial 2	
Partial 3	
Targeted	
Authorisation	

4.5. Effects on product quality

54 For each scenario, please indicate how in your opinion the quality of your products would be affected. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years.

Restriction	Reaction type	Likely consequences
Complete	Immediate	
	In 2-3 years	
Partial 1	Immediate	
	In 2-3 years	

Partial 2	Immediate	
	In 2-3 years	
Partial 3	Immediate	
	In 2-3 years	
Targeted	Immediate	
	In 2-3 years	
Authorisation	Immediate	
	In 2-3 years	

4.6. Effects on competiveness

55 Please indicate effect on competiveness of the different scenarios on your product/business. Solvents like DMF are often used only as possess solvent which is removed at the end of the manufacturing process. Consequently there is competition between imports of final product not containing DMF from Non EU countries. How does this influence EEA competiveness on a global market (e.g. technology transfer of DMF dependent processes requiring DMF to non-EEA countries)?

Restriction	Likely consequences
Complete	
Partial 1	
Partial 2	
Partial 3	
Targeted	
Authorisation	

4.7. Effects on innovation

56 For each scenario, please briefly describe the most likely consequences for innovation. For example, in what way would the switch to an alternative substance affect efforts to improve existing products? In what way, would it affect efforts to develop new products? In what way would it affect efforts to decrease costs or improve efficiency?

Restriction	Reaction type	Likely consequences
Complete	Immediate	
	In 2-3 years	
Partial 1	Immediate	
	In 2-3 years	
Partial 2	Immediate	
	In 2-3 years	
Partial 3	Immediate	
	In 2-3 years	
Targeted	Immediate	
	In 2-3 years	
Authorisation	Immediate	
	In 2-3 years	

4.8. Other effects

57 Please indicate any other information concerning indirect impacts that you consider relevant for the socio-economic analysis of DMF.

Appendices Section G

Annex G1: Questionnaire for DMF Exposure Scenario Building

INFORMATION FOR EXPOSURE SCENARIO BUILDING

(According to ECHA's

Guidance on Information requirements and chemical safety assessment)

Please, fill a different questionnaire for each different Use & Exposure Scenario of the substance.

February 2013

COMPANY	
Adress (Street, City, Country)	
Use-Nº	
Tonnage	
Substance Name:	**Dimethyl Formamide (DMF)**
CAS-Number	**68-12-2**

Is the substance exclusively used in food and/or feedingstuff and/or in medicinal products?

YES	☐	**Not necessary to complete this form. Please inform us in this case.**
NO	☐	**Please fill the q**uestionnaire

1. Use

Industrial users	☐
Professional users	☐
Consumer use	☐

Examples:

Industrial use: manufacturing plant or industrial site.
Professional use: painters, exterminator, building worker, etc.
Consumer use: products for direct use or ownership rather than for resale or use in production and manufacturing.

2. Select from the following table, the sector of use which better describes the activities of your company.

When an appropriate descriptor does not exist in the table, “other” should be selected and a NACE code should be used.

(available at http://ec.europa.eu/comm/competition/mergers/cases/index/nace_all.html)

Descriptors for Sector of use (SoU)		
		Sector of use (SoU)
SU 0-1	☐	Other activity related to manufacturing of chemical products
SU 0-2	☐	Other activity related to manufacture and services
SU 1	☐	Agriculture, forestry, fishery
SU 2	☐	Mining, (including offshore industries)
SU 3	☐	Industrial Manufacturing (all)
SU 4	☐	Manufacture of food products
SU 5	☐	Manufacture of textiles, leather, fur
SU 6	☐	Manufacture of pulp, paper and paper products
SU 7	☐	Printing and reproduction of recorded media
SU 8	☐	Manufacture of bulk, large scale chemicals (including petroleum products)
SU 9	☐	Manufacture of fine chemicals
SU 10	☐	Formulation [mixing] of preparations and/or re-packaging
SU 11	☐	Manufacture of rubber products
SU 12	☐	Manufacture of plastics products, including compounding and conversion
SU 13	☐	Manufacture of other non-metallic mineral products, e.g. plasters, cement
SU 14	☐	Manufacture of basic metals
SU 15	☐	Manufacture of fabricated metal products, except machinery and equipment
SU 16	☐	Manufacture of computer, electronic and optical products, electrical equipment
SU 17	☐	General manufacturing, e.g. machinery, equipment, vehicles, other transport equipment.
SU 18	☐	Manufacture of furniture
SU 19	☐	Building and construction work
SU 20	☐	Health services
SU 21	☐	Private households (= general public = consumers)
SU 22	☐	Public domain (administration, education, entertainment, services, craftsmen)
SU 23	☐	Recycling
Other	☐	Comments:

3. Select from the following table, the type of chemical product which better describes the use of the substance.

When no appropriate descriptor is available “other product” should be selected and a category should be specified in the free text field. It is recommended to make reference to sub-categories covered in the Nordic use categories

http://echa.europa.eu/documents/10162/17224/inforeq_csr_r12_en.pdf

Descriptor for Types of Chemical Product [PC = Product Category]		
PC 0	☐	Other products
PC 1	☐	Adhesives, Sealants
PC 2	☐	Adsorbent
PC 3	☐	Air care products
PC 4	☐	Anti-Freeze and De-icing products
PC 5	☐	Artists Supply and Hobby preparations
PC 6	☐	Automotive Care Products
PC 7	☐	Base metals and alloys
PC 8	☐	Biocidal Products (e.g. Disinfectants, pest control)
PC 9	☐	Coatings and Paints, Fillers, Putties, Thinners
PC 10	☐	Building and construction preparations not covered elsewhere
PC 11	☐	Explosives
PC 12	☐	Fertilizers
PC 13	☐	Fuels
PC 14	☐	Metal surface treatment products, including galvanic and electroplating products,
PC 15	☐	Non-metal-surface treatment products
PC 16	☐	Heat Transfer Fluids
PC 17	☐	Hydraulic Fluids
PC 18	☐	Ink and Toners
PC 19	☐	Intermediate
PC 20	☐	Products such as ph-regulators, flocculants, precipitants, neutralization agents, other unspecific
PC 21	☐	Laboratory Chemicals
PC 22	☐	Lawn and Garden Preparations, including fertilizers
PC 23	☐	Leather tanning, dye, finishing, impregnation and care products
PC 24	☐	Lubricants, Greases and Release Products
PC 25	☐	Metal Working Fluids
PC 26	☐	Paper and Board dye, finishing and impregnation products
PC 27	☐	Plant Protection Products

Descriptor for Types of Chemical Product [PC = Product Category]		
PC 28	☐	Perfumes, Fragrances
PC 29	☐	Pharmaceuticals
PC 30	☐	Photochemicals
PC 31	☐	Polishes and Wax Blends
PC 32	☐	Polymer Preparations and Compounds
PC 33	☐	Semiconductor
PC 34	☐	Textile dyes, finishing and impregnating products
PC 35	☐	Washing and Cleaning Products (including solvent based products)
PC 36	☐	Water softeners
PC 37	☐	Water treatment chemicals
PC 38	☐	Welding and soldering products, flux products
PC 39	☐	Cosmetics, personal care
PC 40	☐	Extraction agents
Others	☐	Comments:

4. Select from the following table, the process category which better describes the use of the substance.

Descriptor for process categories [PROC]			
Descriptor			Examples and explanations
PROC 0	☐	Other process	
PROC 1	☐	Use in closed process, no likelihood of exposure	Use of the substances in high integrity contained system where little potential exists for exposures, e.g. any sampling via closed loop systems.
PROC 2	☐	Use in closed, continuous process with occasional controlled exposure	Continuous process but where the design philosophy is not specifically aimed at minimizing emissions. It is not high integrity and occasional expose will arise, e.g. through maintenance, sampling and equipment breakings.
PROC 3	☐	Use in closed batch process (synthesis or formulation)	Batch manufacture of a chemical or formulation where the predominant handling is in a contained manner, e.g. through enclosed transfers, but where some opportunity for contact with chemicals occurs, e.g. through sampling

Descriptor for process categories [PROC]			
PROC 4	☐	Use in batch and other process (synthesis) where opportunity for exposure arises	Use in batch manufacture of a chemical where significant opportunity for exposure arises, e.g. during the charging, the sampling or discharge of material, and when the nature of the design is likely to result in exposure.
PROC 5	☐	Mixing or blending in batch processes (multistage and/or significant contact)	Manufacture or formulation of chemical products or articles using technologies related to mixing and blending of solid or liquid materials, and where the process is in stages and provides the opportunity for significant contact at any stage.
PROC 6	☐	Calendering operations	Processing of product matrix Calendering at elevated temperature an large exposed surface
PROC 7	☐	Industrial spraying	Air dispersive techniques Spraying for surface coating, adhesives, polishes/cleaners, air care products, sandblasting; Substances can be inhaled as aerosols. The energy of the aerosol particles may require advanced exposure controls; in case of coating, overspray may lead waste water and waste.
PROC 8	☐	Transfer of chemicals from/to vessels/large containers at non dedicated facilities	Sampling, loading, filling, transfer, dumping, bagging in non dedicated facilities. Exposure related to dust, vapour, aerosols or spillage, and cleaning of equipment to be expected.
PROC 9	☐	Transfer of chemicals into small containers (dedicated filling line)	Filling lines specifically designed to for both, capturing vapour and aerosol emissions and minimise spillage
PROC 10	☐	Roller application or brushing	Low energy spreading, Including cleaning of surfaces. Substance can be inhaled as vapours, skin contact through droplets, splashes, working with wipes and handling of treated surfaces.
PROC 11	☐	Non industrial spraying	Air dispersive techniques Spraying for surface coating, adhesives, polishes/cleaners, air care products, sandblasting; (also includes manufacture of foam, including blowing operations) Substances can be inhaled as aerosols. The energy of the aerosol particles may require advanced exposure controls; in case of coating, overspray may lead waste water and waste.
PROC 12	☐	Use of blow agents for foam production	

Descriptor for process categories [PROC]			
PROC 13	☐	Treatment of articles by dipping and pouring	Immersion operations Treatment of articles by dipping, pouring, immersing, soaking, washing out or washing in substances; including cold formation or resin type matrix. Includes handling of treated objects (e.g. after dying, plating,), Substance is applied to a surface by low energy techniques as dipping the article into a bath or pouring a preparation onto a surface.
PROC 14	☐	Production of preparations or articles by tabletting, compression, extrusion, pelettisation	
PROC 15	☐	Use of laboratory reagents in small scale laboratories	Use of substances at small scale laboratory (1 l or 1 kg). Larger laboratories and R+D installations should be treated as industrial processes.
PROC 16	☐	Using material as fuel sources, limited exposure to unburned product to be expected	Covers the use of material as fuel sources (including additives) where limited exposure to the product is its unburned form is expected. Does not cover exposure as a consequence of spillage or combustion.
PROC 17	☐	Lubrication at high energy conditions and in partly open process	Lubrication at high energy conditions (temperature, friction) between moving parts and substance; significant part of process is open to workers or to the environment The metal working fluid may form aerosols or fumes due to rapid moving metal parts; exhausted cutting fluids need to be disposed off as waste
PROC 18	☐	Greasing at high energy conditions	Use as lubricant where significant energy or temperature is applied between the substance and the moving parts.
PROC 19	☐	Hand-mixing with intimate contact (only PPE available	Addresses occupations where intimate and intentional contact with substances occurs without any specific exposure controls than PPE.
PROC 20	☐	Heat and pressure transfer fluids (closed systems) in dispersive use	Motor and engine oils, brake fluids Also in these applications, the lubricant may be exposed to high energy conditions and chemical reactions may take place during use. Exhausted fluids need to be disposed of as waste. Repair and maintenance may lead to skin contact. Leakage during use may lead to environmental exposure.
PROC 21	☐	Low energy manipulation of substances bound in materials and/or articles	Manual cutting, rolling or assembly of material/article, possibly resulting in the release of fibres or rubber fumes;
PROC 22	☐	Potentially closed operations with minerals at elevated temperature	Activities at smelters, furnaces, refineries, coke ovens. Exposure related to dust and fumes to be expected. Emission of direct cooling may be relevant.

Descriptor for process categories [PROC]			
PROC 23	☐	Open processing and transfer of minerals at elevated temperature	Sand and die casting, tapping and casting melted solids, raking melted solids paving; Exposure related to dust and fumes to be expected. Emission of direct cooling may be relevant.
PROC 24	☐	High (mechanical) energy work-up of substances bound in materials and/or articles	Substantial thermal or kinetic energy applied to substance by grinding, mechanical cutting, drilling or sanding. Release of solids (dust) or fumes to be expected
PROC 25	☐	Hot work operations with metals	Welding, soldering, gouging, brazing, flame cutting Exposure due to the release of fumes to be expected.
Comments	☐		

5. In case of substances contained in articles, select from the following table, the type of the article.

Table 5.1: Substances in articles with not intended release

Descriptors for substances in articles with no intended release [AC]		
AC 0	☐	Other Articles
AC 1-1	☐	Passenger cars and motor cycles
AC 1-2	☐	Other vehicles: Railway, aircraft, vessels, boats, trucks, and associated transport equipment
AC 2	☐	Machinery and mechanical appliances thereof
AC 3-1	☐	Electrical and electronic products, e.g. computers, office equipment, video and audio recording, communication equipment
AC 3-2	☐	Electrical batteries and accumulators
AC 3-3	☐	Electrical and electronic products: Household appliances (white ware)
AC 3-4	☐	Photographic and reprographic articles: cameras, video cameras
AC 4	☐	Glass and ceramic products: dinner ware, pots, pans, food storage containers
AC 5-1	☐	Fabrics, textiles and apparel: bedding and clothing
AC 5-2	☐	Fabrics, textiles and apparel: curtains, upholstery, carpeting/flooring, rugs,
AC 6	☐	Leather products: apparel and upholstery
AC 7-1	☐	Metal products: cutlery, cooking utensils, pots, pans,
AC 7-2	☐	Metal products: toys
AC 7-3	☐	Metal products: furniture
AC 8-1	☐	Paper products: tissue, towels, disposable dinnerware, nappies, feminine hygiene products, adult incontinence products, writing paper
AC 8-2	☐	Paper products: newspaper, packaging

Descriptors for substances in articles with no intended release [AC]		
AC 9	☐	Photographic and reprographic articles: films, printed photographs
AC 10-1	☐	Rubber products: tyres
AC 10-2	☐	Rubber products: flooring
AC 10-3	☐	Rubber products: footwear
AC 10-4	☐	Rubber products: toys
AC 10-5	☐	Other general rubber products
AC 11-1	☐	Wood and wood furniture: flooring
AC 11-2	☐	Wood and wood furniture: furniture
AC 11-3	☐	Wood and wood furniture: toys
AC 12-1	☐	Constructional articles and building material for indoor use: wall construction material ceramic, metal, plastic and wood construction material, insulating material.
AC 12-2	☐	Constructional articles and building material for outdoor use: wall construction material, road surface material, ceramic, metal, plastic and wood construction material, insulating material.
AC 13-1	☐	Commercial/consumer plastic products like disposable dinner ware, food storage, food packaging, baby bottles
AC 13-2	☐	Plastic products: Flooring
AC 13-3	☐	Plastic products: Toys

Table 5.2: Substances in articles with intended release

Descriptors for substances in articles with intended release [AC]		
AC30	☐	Other articles with intended release of substances
AC31	☐	Scented clothes
AC32	☐	Scented eraser
AC34	☐	Scented toys
AC35	☐	Scented paper articles
Descriptors for substances in articles with intended release [AC]		
AC36	☐	Scented CD
AC37	☐	Other scented articles
AC38	☐	Packaging material for metal parts, releasing grease/corrosion inhibitors
AC39	☐	Other articles releasing grease or corrosion inhibitors
Comments	☐	

6. Select from the following table, which best describes environmental exposure

Descriptors for Environmental Release Classes [ERC]		
ERC1	☐	Production of chemicals
ERC2	☐	Formulation of preparations
ERC3	☐	Formulation in materials
ERC4	☐	Industrial use of processing aids
ERC5	☐	Industrial use resulting in inclusion into or onto a matrix
ERC6A	☐	Industrial use of intermediates
ERC6B	☐	Industrial use of reactive processing aids
ERC6C	☐	Production of plastics
ERC6D	☐	Production of resins/rubbers
ERC7	☐	Industrial use of substances in closed systems
ERC8A	☐	Wide dispersive indoor use of processing aids in open systems
ERC8B	☐	Wide dispersive indoor use of reactive substances in open systems
ERC8C	☐	Wide dispersive indoor use resulting in inclusion into or onto a matrix
ERC8D	☐	Wide dispersive outdoor use of processing aids in open systems
ERC8E	☐	Wide dispersive outdoor use of reactive substances in open systems
ERC8F	☐	Wide dispersive outdoor use resulting in inclusion into or onto a matrix
ERC9A	☐	Wide dispersive indoor use of substances in closed systems
ERC9B	☐	Wide dispersive outdoor use of substances in closed systems
ERC10A	☐	Wide dispersive outdoor use of long-life articles and materials with low reléase
ERC10B	☐	Wide dispersive outdoor use of long-life articles and materials with high or intended reléase
ERC11A	☐	Wide dispersive indoor use of long-life articles and materials with low reléase
ERC11B	☐	Wide dispersive indoor use of long-life articles and materials with high or intended reléase
Comments	☐	

7. Temperature of the process.

	ºC

8. Duration and frequency of exposure

Indicate the frequency (e.g.: days per week) and the duration (hours/day) of the exposure to the substance.

Duration and frequency of exposure:	
5 days per week	☐
4 hours/day	☐
8 hours/day	☐
Other (specify):	

9. Information on the exposure to the substance in preparations or articles

Indicate the concentration of the substance, the physical state of the preparation and the applied amount of the substance.

Concentration of the substance:
Physical state:
Applied amount of the substance (per application, per time or per activity)
Indoor or outdoor use (describe):

10. Risk Management measures for Human Health

10.1 - Technical measures	
Open process	☐
Closed process	☐
Automated process	☐
General ventilation	☐
Local exhaust ventilation	☐
Other (specify):	

10.2 - Organisational measures	
Limiting the time of operations/activities (specify)	
Other (specify):	

10.3 - Personal protection measures	
Gas filter masks	☐
Dust filter masks	☐
Goggles	☐
Gloves	☐
Protective clothing (describe):	
Other (specify):	

10.4 - Consumer related measures	
Form of packaging (describe):	
Migration-preventing coating (describe):	

Other (specify):

11. Risk management measures for effluents and waste

11.1 <u>For liquid waste</u>

Emission to a sewage treatment plant	No☐	Yes☐	
Quantity			liters/day
Concentration (units)			/
Duration of emission			days/year

If known, specify the type of sewage treatment (physico-chemical treatment, biological treatment, etc.):

11.2 <u>For solid waste or gaseous waste</u>, describe the type of treatment:

Quantity		/day
Concentration		/
Duration of emission		days/year

12. Other data (e.g. workplace measurements):

Please fill in and return as soon as possible to:

Chemservice S.A.
Dr. Günter Spang
5, an de Laengten
L-6776 Grevenmacher

Phone: +352 270776-1
Fax: +352 270776-75

Mail: **g.spang@chemservice-group.com**

Thank you very much for your cooperation!!!

Annex G2: Extended Questionnaire regarding Identified Uses of DMF

Dated: 2nd August 2013

DMF_IdentifiedUses_
Questionnaire2_Augu

Annex G3: Questionnaire on DMF in Articles from Italian CA to Member States

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Questionnaire for the EU Member States on N,N-Dimethylformamide (in the following DMF)

CAS-No.: 68-12-2

Foreword

Italian Competent Authority (Ministry of Health) is going to prepare a Restriction Dossier on DMF for Annex XV of the Reach Regulation.

This questionnaire is therefore intended to collect information from other Member States related to possible restriction of DMF in articles as well as to collect information from customs and consumers, if available from each Member States.

Please kindly answer to the following question at your best knowledge; your information/data will be very useful to assess the restriction proposal.

Questionnaire

1. Any proof of existence of articles containing DMF?
2. In case of confirmation, which kind of articles? Please describe.
3. What was identified concentration of DMF in relevant articles?
4. Are concentration limits available for certain articles?
5. Is information on migration rates of DMF in different matrices available?
6. Please describe any experience regarding analytical methods for DMF concentration detection in different matrices of articles.
7. Different handling and risk management of articles for consumers/public and workers?
8. Do you have any data/information from customs regarding controls of articles containing DMF?
9. Do you have any data/information from consumers regarding the use of articles containing DMF?
10. Any other available information?

Best regards

Dr. Pietro Pistolese
Italian Ministry of Health (Competent Authority)